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Pulmonary Tuberculosis: Mortality after Sanatorium Treatment

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INTRODUCTION

THE King Edward VII Sanatorium at Midhurst, Surrey, was opened for the reception of patients in July 1906. The Council of the Sanatorium realized from the first the importance of tracing as far as possible the after-history of every case treated there, in order to collect evidence by which a true judgement of the value of sanatorium treatment might be formed. They introduced therefore a regular system of communication with patients after their discharge by which their states of health were ascertained at regular intervals. As the number of former patients with whom it was necessary to keep in touch increased, the work involved became correspondingly larger and more costly. In 1914 the Medical Research Committee, who were then engaged in framing general schemes of research into tuberculosis, were glad to take advantage of the opportunity offered at Midhurst, and made an annual grant towards the expenses of this inquiry. With the assistance this provided, a special clerk was engaged at Midhurst, whose whole time was given to maintaining correspondence with former patients and to tracing by various means those who had failed to reply to the communications addressed to them. The proportion of patients lost sight of has been thus reduced to 3·5 per cent.

The Medical Research Committee desire in the first place to express their great indebtedness to the Council of the King Edward VII Sanatorium for making the present inquiry possible and giving it their fullest support and encouragement at every step, but no less for permitting this full and early statement of the results achieved. The inquiry itself has been in the hands of Dr. Noel Bardswell, who laid down the lines of investigation to be followed and supervised the laborious work of maintaining the accuracy of the information collected. In the expression of the results he has had the collaboration of Mr. J. H. R. Thompson, who is responsible for the actuarial work. To both these authors the Committee would express their thanks for the preparation of the Report.

The method used is that adopted by Elderton and Perry in their study of the data obtained from the Adirondack Sanatorium. The

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patients are classified in various ways, and the numbers of deaths in each class are compared with the numbers which would be expected in the same period had the classes been samples of the general population corresponding as to age and sex.

In general the mortality found among the Midhurst patients exceeds by amounts which vary from class to class the expectation of what it would have been in equivalent samples of the general population; and this is taken to show that sanatorium treatment did not in fact restore the patients who formed the subject of the investigation to the average condition of health enjoyed by the general population. It would not, however, be just to depreciate the value of sanatorium treatment on this ground. The only statistical criterion of the absolute value of sanatorium treatment would be given by a comparison between the rates of mortality of sanatorium patients and those of tuberculous persons who were similar in age, sex, and economic position, but treated on other lines or untreated. No such comparison can yet be instituted, and the results of the present enquiry are not inconsistent with a belief in the utility of sanatorium treatment.

A section of the present Report gives the results observed at Midhurst of the treatment of pulmonary tuberculosis with tuberculin, of which the value has long been a matter of controversy. It will be seen that the results actually obtained show that tuberculin treatment, as practised at Midhurst according to methods described in the Report, and when given in addition to the usual course of sanatorium treatment, had no appreciable effect, either favourable or unfavourable. The authors describe their conclusions as to the value of tuberculin as being 'distinctly disappointing', but it must be remembered that the negative results obtained here followed the administration of tuberculin by one selected method and system of dosage, and the only conclusion that can properly be drawn from the results now presented is that this method of treatment as practised in that manner at Midhurst did not give any evidence of its value.

Medical Research Committee,
15 Buckingham Street,
Strand, W.C. 2.

June 21, 1919.

PULMONARY TUBERCULOSIS.
MORTALITY AFTER SANATORIUM TREATMENT

A REPORT ON THE EXPERIENCE OF THE KING EDWARD VII SANATORIUM, MIDHURST

BY

NOEL D. BARDSWELL, M.V.O., M.D., F.R.C.P.

Late Medical Superintendent King Edward VII Sanatorium
Medical Advisor to the Insurance Committee for the County of London

AND

JOHN H. R. THOMPSON, F.I.A.

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INTRODUCTION.

DURING the past ten years the control of tuberculosis has come increasingly into general notice as one of the pressing health questions of the day. Interest in the subject, already considerable, was quickened by the passing of the National Insurance Acts, which offered substantial assistance to measures undertaken for the pre-

vention and treatment of the disease. Since that date, owing to the initiative of public authorities and private philanthropy, institutions for the treatment of tuberculous persons have been multiplied throughout the country, effecting a change, almost revolutionary in character, upon the conditions hitherto existing. Although much has been accomplished, the control of tuberculosis is far from realized, and there can be no doubt that the near future will see further efforts directed towards the betterment of our present means alike of prevention and treatment. As a preliminary to the preparation of new schemes or to the extension of the scope of those which already exist, it is desirable that the results so far obtained should be examined; the more so since, in the absence of previous experience, the measures adopted have been somewhat experimental in character. Among other issues, the economic value of the institutional treatment of pulmonary tuberculosis, a subject upon which experienced opinion is much divided, needs, if possible, to be determined. But the truth is not easy to arrive at. It is not possible to make any direct estimate of the economic return to the community of the work performed by patients after treatment in a sanatorium.

However, the extent to which a number of tuberculous patients, subsequent to their discharge from a sanatorium, were capable of following their ordinary occupation, and by their work adding to the general wealth of the nation, should find some reflection in the mortality rate experienced by them. A comparison of their mortality with that of the general population gives, at least, an indication as to how far the treatment at the sanatorium resulted in the permanent restoration of capacity for work.

In the investigation detailed in this report, the experience of patients after treatment in the King Edward VII Sanatorium has been studied from this point of view; their rates of mortality have been determined, and the results compared with the rates which prevail in the general community.

The object of the research, primarily, was to ascertain the degree of permanent benefit which patients suffering from various degrees of pulmonary tuberculosis may be expected to derive from treatment in a sanatorium, but as the work progressed, its scope was broadened. The original inquiry and the subsidiary investigations are described in detail later. At this point they may be summarized with advantage, as an indication of the main lines of the Report:

(1) The mortality experienced by patients suffering from pulmonary tuberculosis in its various stages: (*a*) Condition on admission; (*b*) Condition on discharge.

(2) The mortality experienced by patients who were treated with tuberculin.

(3) The mortality experienced by patients whose illness began insidiously, with an attack of haemoptysis or with symptoms of pleurisy.

(4) The mortality experienced by patients from whose sputum tubercle bacilli (*a*) did, and (*b*) did not, disappear during their treatment in the sanatorium.

(5) The mortality experienced by patients who presented evidence of tuberculosis of the larynx.

(6) The mortality experienced by patients who gave a family history of tuberculosis.

Social Condition.

In connexion with an investigation of this character, the consideration of the social stratum from which patients are drawn is of importance, for the better the facilities for living under good conditions, the more hopeful the prospects of recovery.

It should be stated then that the patients whose records are reviewed in this report represent such professions and occupations as those of clerk, school teacher, shopkeeper, clergy of all denominations, engineer, civil servant, solicitor, medical practitioner, accountant, commercial traveller, hospital nurse, governess, secretary, &c.

The proportionate representation of these various professions varied little from year to year. The patients were people of comparatively small means; in the case of the men, and many of the women, they were dependent upon their own exertions for a livelihood.

The well-to-do, and those belonging to the artisan, the domestic servant, and to the working or industrial classes, are not eligible for treatment at the King Edward VII Sanatorium.

Clinical Condition.

Selection of Cases for Treatment.

An endeavour is made to admit to the sanatorium only those patients who are suffering from pulmonary tuberculosis in its earlier stages, and who, to all appearances, have a good prospect of recovery. The patients are selected inasmuch as preference is given to the more favourable; those clearly in an advanced stage are not accepted. Applicants for admission who live within easy access of London are examined by the Medical Superintendent, but in the case of those who live at a distance, the decision as to their suitability is made upon information furnished by medical practitioners. As will be shown later, the annual admissions always include a proportion of somewhat advanced cases.

Classification of Cases.

The cases have been grouped in accordance with the following system of classification, which is that adopted by the Association for the Study and Prevention of Tuberculosis in America:

Group 1. Incipient cases. Slight or no constitutional symptoms, particularly gastric or intestinal disturbances, or rapid loss of weight.

Slight or no elevation of temperature, or acceleration of pulse at any time during the twenty-four hours.

Expectoration small in amount or absent. Tubercle bacilli may or may not be present.

Slight infiltration limited to the apex of one or both lungs, or a small part of one lobe.

No tuberculous complications.

Group 2. Moderately advanced cases. No marked impairment of function, either local or constitutional.

Marked infiltration, more extensive than in the incipient cases, but with little or no evidence of cavity formation.

No serious tuberculous complications.

Group 3. Far advanced cases. Marked impairment of function, local and constitutional.

Extensive infiltration or consolidation in one or more lobes, or disseminated areas of cavity formation, or serious tuberculous complications.

This method of grouping closely resembles the Turban and Turban-Gerhardt systems of classification. It differs from them in that constitutional symptoms are taken into account in addition to the anatomical distribution of the disease in the lungs.

The following terms are used to describe the condition of patients on discharge from the sanatorium:

'ARRESTED': General health completely restored in every respect without any sign of disease of the lungs except such as is compatible with a completely healed lesion. Sputum, if still present, free from tubercle bacilli.

'MUCH IMPROVED': General health good. Physical signs of disease in the lungs, though much diminished, not entirely cleared up, e.g. perhaps limited to a few crepitations on cough only. Tubercle bacilli still to be detected in the sputum.

'IMPROVED': General health improved, but not restored. Physical signs of disease in the lungs, though less marked than on admission, still present.

'STATIONARY': No appreciable improvement in the condition of the lungs or in the general health.

'WORSE': General or local condition worse.

The Treatment adopted at the Sanatorium.

The treatment received by the patients at the sanatorium consists of the combination of hygienic measures, generally understood by the term 'sanatorium treatment'; the details of this method are sufficiently well known to require no particular description. With the exception of the use of tuberculin during the years 1912, 1913, and 1914, the treatment adopted, apart from that directed to the alleviation of special symptoms, consisted of general hygienic measures.

Duration of Treatment in the Sanatorium.

The duration of residence in the sanatorium varied from a minimum of eight weeks to a maximum of twelve months: the average length of stay was about five months. A proportion of the patients continued treatment after discharge either at home or in other institutions: this after-treatment has not been included in the estimate of duration of residence in the sanatorium.

The Method adopted to obtain 'After-Histories'.

Every year a circular is sent out asking for the following information:

1. What is your present state of health?
2. Are you at work? If so, what are you doing?
3. Have you had any break-downs since last writing to me?
4. How far are you carrying on the treatment?
5. Have you heard of any patients who were contemporary with you at the sanatorium?

The majority of reports come to hand in the course of a few months, the remainder, for the most part, are received irregularly throughout the rest of the year. The request for news of contemporaries often secures a clue as to the whereabouts of a patient who has not answered. Should these methods of inquiry not meet with success information is sought of medical practitioners, employers, and others who were known to have been in touch with a patient when in the sanatorium. In the event of this step proving fruitless, a personal inquiry is made in the neighbourhood from which a patient sent his last report; for example, useful information can often be obtained at the local shops. Finally, the death returns of the Registrar-General are consulted.

The systematic tracing of patients entails considerable amount of work and presents many difficulties. Up till 1914, the patients 'lost sight of' averaged 9 to 10 per cent.; since that date the annual grant received from the Medical Research Committee has allowed of a more thorough search, with the result that with the exception of 3·5 per cent. the 'after-history', up till the present time, has been obtained for every patient discharged from the sanatorium since it was opened in July 1906.

The value of statistics published in reports of sanatoriums is reduced materially by the fact that a large proportion of the cases dealt with are returned as 'lost sight of', 'condition unknown'. In the case of institutions which treat the working classes the tracing of patients is obviously difficult. However, the experience of the King Edward VII Sanatorium suggests that if the search for 'after-history' records be prosecuted thoroughly a considerable measure of success may be achieved.

The Data upon which the Report is based.

The data with which this report deals consist of the records of 1,707 patients who were discharged from the sanatorium during

the eight years 1907–14. Of this number, 1,053 were males and 654 females. The only patients discharged during these years, who have not been included in the investigation, are those who remained in the sanatorium for less than eight weeks. The patients thus excluded fall into two classes:

(*a*) Those whose condition on admission was found to be hopeless and who therefore were unsuitable for treatment in the institution.

(*b*) A few patients who for various reasons were able to stay at the sanatorium for a few weeks only.

Neither of these groups of patients can be said to have received a course of treatment in the sanatorium. Patients who received less than eight weeks' treatment but who returned at a later date and remained for more than eight weeks are included, but the first visit has not been taken into account. Those whose residence extended beyond eight weeks and who returned to the sanatorium at a later date for a second course of treatment are deemed to come under observation as at the earlier period. For the purposes of analytical treatment the data are not so extensive as might be wished: this is a defect inherent in many statistics of a special nature such as those now presented. In making the deductions given in the report, the paucity of the data upon which the mortality rates are based, has not been lost sight of. It is thought, however, that the results are in the main sufficiently striking in themselves to warrant considerable weight being attached to them. In some instances confirmatory evidence is forthcoming from the work of previous investigators in this important sphere of vital statistics; such corroboration is valuable and strengthens considerably the conclusions arrived at.

Number and Sex of Patients discharged during the Successive Years.

The following Table I shows the number of patients discharged in each of the eight years; the males and females are given separately. In order to facilitate a comparison the percentages are also given:

TABLE I

Patients Discharged each Year.

Year	Number Discharged			Percentage of each Sex		Percentage of total number of Patients	
	Male	Female	Total	Male	Female	Male	Female
1907	129	79	208	62·0	38·0	12·2	12·1
1908	147	96	243	60·5	39·5	14·0	14·7
1909	143	90	233	61·4	38·6	13·6	13·7
1910	131	75	206	63·6	36·4	12·4	11·5
1911	140	85	225	62·2	37·8	13·3	13·0
1912	102	62	164	62·2	37·8	9·7	9·5
1913	117	78	195	60·0	40·0	11·1	11·9
1914	144	89	233	61·8	38·2	13·7	13·6
Total	1053	654	1707	61·7	38·3	100·0	100·0

It will be noticed that, of the patients discharged from the sanatorium, about 62 per cent. were males and 38 per cent. females, these proportions being practically constant throughout the whole eight years during which the discharges occurred.

Further, as between the sexes the percentage of patients discharged does not in respect of any particular year appear sensibly to vary from the average for the period as a whole. When comparing the mortality experience of the sexes these points are of considerable importance, since, as will be shown subsequently, the excess mortality is a function of the number of years elapsed since discharge.

Age of Patients as at the Date of Discharge.

The ages of the patients as at the date of discharge vary between 14 and 66. These data have for convenience been divided into six age groups ; the numbers in each group are given below in Table II with the corresponding percentages.

The latter indicate that the proportion of males to females in each group vary but little as compared with the proportion obtained by taking the whole of the patients together. Some significance attaches to the incidence of the age of attack, since, as hereinafter shown, the excess mortality is demonstrably heavier at the younger ages at discharge.

TABLE II

Age Group	Number of Patients discharged in each Age Group			Percentage of Patients discharged in each Age Group	
	Male	Female	Total	Male	Female
-22	127	77	204	62·3	37·7
23-27	249	166	415	60·0	40·0
28-32	219	157	376	58·2	41·8
33-37	185	107	292	63·4	36·6
38-42	120	70	190	63·2	36·8
43-	153	77	230	66·5	33·5
Total	1053	654	1707	61·7	38·3

The age at which the maximum number of discharges occur is 25 for both male and female patients. The graphs exhibited in Diagram 1 demonstrate that the age distribution of each sex is closely comparable throughout the whole range of ages. It may be noted that, since the age is in all cases the age at discharge, the graphs do not represent the ages at onset of the disease ; the latter may be taken approximately as having occurred about two years earlier.

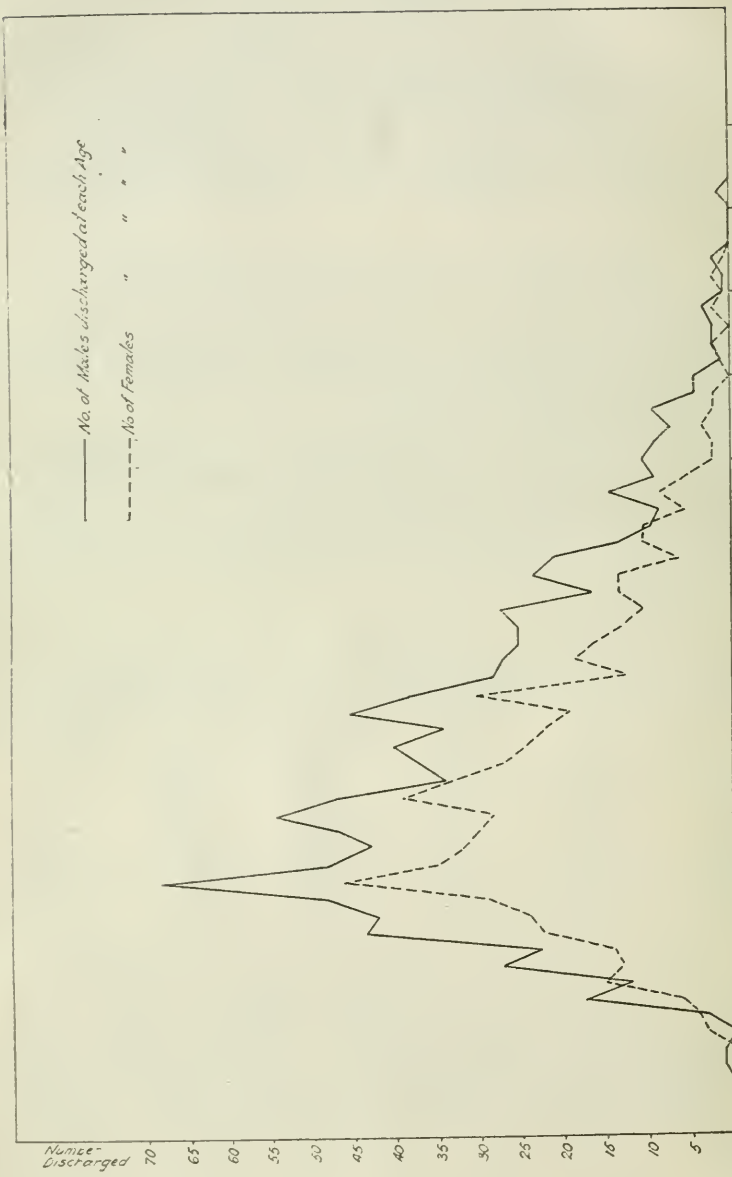
No. of Males discharged at each Age
No. of Females " " "
Number Discharged
AGE last B.D. at discharge

Diagram 1.

The Tabulation of the Data.

As a preparatory measure a card was prepared giving particulars in respect of each patient who had been discharged from the sanatorium during the eight years 1907–14 inclusive. In order to distinguish the sexes, a white card was used for the male patients, and a buff card for the female patients.

A facsimile of both sides of the card is given below.

Facsimile of Card.

recto

KING EDWARD VIITH SANATORIUM

EXPERIENCE

FEMALES 1907–1916 No. . . . . .

	Year	Month	Day
Date of Admission			
Date of Discharge			
Duration of Treatment			
Date 'last heard of'			
Date of Death			
Age last Birthday at Admission			
Age at Discharge			
Duration at Exit			
Age at Exit			

Mode of Exit_____

Remarks :

verso

MEDICAL CLASSIFICATION

Condition on Admission :
- Group 1 Early Stage
- ,, 2 Moderately Advanced
- ,, 3 Advanced_____

Condition on Discharge :
- (*a*) Arrested
- (*b*) Much Improved
- (*c*) Improved
- (*d*) Stationary or Worse_____

Type of Onset :
- (*a*) Haemoptysis
- (*b*) Pleurisy
- (*c*) Cough, Loss of Weight_____

Examination of Sputum on Admission & Discharge_____

+ +, + −, − −

Has the Larynx been infected ?_____

Was Tuberculin given in 1912, 1913, or 1914? _____

Weight Normal___ Height_____

At Admission___

At Discharge____

Is there a History of Tuberculosis? _____

The details of the medical classifications and the following particulars for the experience side of tbe card were obtained from the after-history registers at the sanatorium :

No. in after-history register.
Date of admission.
Age at admission.
Date of discharge.
Date 'last heard of'.
Date of death.

With the aid of this information the experience side of the cards was completed.

Among the patients who died there were six for whom the cause of death was recorded as 'killed in action' or 'died of injuries received in France'. For the purpose of this investigation it would not be proper to include these cases among the deaths, since at the date of death they were presumably in good health. A better representation of the facts is obtained by tabulating each of them as 'lost sight of' at the date of death. This course was therefore adopted.

Since the number of patients discharged in each year of age was comparatively small, it is not necessary or even advisable to consider each age at discharge separately. The examination of the mortality experience is better served by grouping successive ages together, and assuming that all patients discharged at these ages have been discharged at a central or average age. In favour of grouping the ages it may be mentioned that the influence of an increase of one year in the age is generally of less importance than a similar increase in the duration or number of years elapsed since discharge.

As previously stated the ages at discharge were divided into six groups; the groups being the same for males as for females. By an examination of the number of cases included in each group of ages the average ages were ascertained, and except for the last group they were identical for both sexes. In regard to the group of ages '43 and upwards' it was found that a more correct result would be obtained by adopting age 50 for the males and age 49 for the females.

Particulars of these groupings are given in Table III.

TABLE III

Number of Group	Ages included in Group	Average Age of Group	
		Males	Females
1	-22	20	20
2	23-27	25	25
3	28-32	30	30
4	33-37	35	35
5	38-42	40	40
6	43-	50	49

The 'exposed to risk' was calculated in respect of each group of ages for each year elapsed since discharge from the sanatorium. Since the 'exposed to risk' form the statistical basis of the whole Report, the methods adopted in its calculation are of considerable importance. It was thought that the elaboration of the actual analytical processes to which the data were subjected would be of interest to other observers of vital statistics of this nature; accordingly a full account is detailed in Appendix B. It may, however, be briefly stated that each patient was observed from the date of discharge and traced through each successive year of discharge until the year of death, the date 'last heard of', or the date of closing of observations. The latter, in the case of the survivors, was in every instance the anniversary of discharge in 1916.

The method adopted to ascertain the mortality experience was to

compare the number of actual deaths with the expected deaths, calculated by multiplying the exposed to risk by the rates of mortality for the appropriate ages according to a standard table of mortality.

The standard table selected for this purpose was the English Life Table, No. 8, as being the latest exponent available of general population mortality. This table was based upon the population of England and Wales enumerated at the last census in 1911, and the deaths of the three years 1910, 1911, and 1912, obtained from the returns of the Registrar-General. Since the mortality rates shown by this table for males are higher than those for females, the expected deaths were calculated by using the rates of mortality appropriate to the particular sex.

The mortality experience in the various classifications is estimated by reference to the several ratios obtained by dividing the actual number of recorded deaths by those expected according to the standard table.[1]

Attention may be drawn to the fact that the comparison made is between the mortality of persons suffering from pulmonary tuberculosis and that of the general population. The latter consists of persons in varied degrees of health, many of whom are consumptive. In fact, a large percentage of the deaths occurring in the general population are the result of tuberculous diseases. If the comparisons had been made with the mortality of exclusively healthy lives, the ratios exhibited would have been considerably higher. Probably the only available rates of mortality applicable to healthy lives are those constructed from the records of the life assurance offices. It was thought, however, that the test of a table like the British Offices' Life Tables, 1893, would in the present instance prove unsuitable.

It is important, therefore, in interpreting the results presented in the Report that due regard should be paid to the inherent characteristics of the general population mortality table.

The Arrangement of the Tables.

In the course of the investigation it was necessary to construct a number of statistical tables of various descriptions involving the rearrangement of the data in several different ways.

A complete set of the summaries of these tables is included in Appendix A. In some cases, where the results were considered of sufficient importance, the tables are given in full. In order to facilitate comparisons, the tables for both sexes are set out side by

[1] The method of comparing Actual Deaths with Expected Deaths has been frequently used by actuaries in making investigations regarding abnormal mortality. In this connexion may be mentioned the Medico-Actuarial Mortality Investigation conducted by the Actuarial Society of America, and also the investigation made by Messrs. Elderton and Perry into the experience of the Adirondack Sanitarium.

It should, however, be noted that the effect of this method of comparison is to indicate the relative mortality which would be experienced in a single year were all the lives exposed to risk simultaneously. This mortality must not be confused with the mortality experienced by a body of lives over a period of years, although the data themselves may have reference to several years.

side for each classification, and are numbered consecutively with arabic numerals.

For the purpose of emphasizing many points brought out during the course of the investigation various subsidiary tables have been extracted, modified, or entirely reconstructed: most of these are given as insets to the Report.

Several diagrams are also given; these it is hoped will be found not only interesting, but useful aids to the study of the results presented.

Owing to the volume of space that would be required, the primary working schedules have not been included in the Appendix. Careful examination was made of these schedules in order that nothing of practical importance or interest should be omitted. A perusal of the various tables both in the Report itself and in the Appendix will, it is thought, disclose the care which was exercised in this matter.

CHAPTER I

Mortality Experience determined according to the Condition on Admission.

It scarcely needs to be stated that the prospects of recovery enjoyed by a number of patients suffering from pulmonary tuberculosis vary greatly; and that while many of those in whom the disease is still in its initial phases have a good prognosis, the outlook of those in whom the morbid process has reached an advanced stage is most unfavourable. For this reason it is customary, for statistical purposes, to classify patients on admission to a sanatorium in accordance with the severity of their disease.

As previously stated the method of classification employed in this report is that adopted by the Association for the Study and Prevention of Tuberculosis in America.

Although the three groups into which patients are classified by this method are sufficiently defined to render them distinct, there must necessarily be many border-line cases rendering the category to which they should be assigned a matter of opinion. It is, therefore, of some importance to note that one medical officer (Dr. Bardswell) is responsible for the whole of the clinical data upon which this report is based.

The data are analysed into the three groups in Table IV.

Table IV

Total Number of Patients 1,707.

No. of Males 1,053					*No. of Females 654*			
No. of Patients in Group on Admission				Age Group	No. of Patients in Group on Admission			
1	2	3	All		1	2	3	All
48	61	18	127	–22	20	33	24	77
72	124	53	249	23–27	46	81	39	166
69	106	44	219	28–32	50	61	46	157
47	99	39	185	33–37	28	55	24	107
20	76	24	120	38–42	13	40	17	70
33	75	45	153	43–	14	37	26	77
289	541	223	1053	Total	171	307	176	654

Percentage of Patients in Group on Admission				Age Group	Percentage of Patients in Group on Admission			
1	2	3	All		1	2	3	All
4·6	5·8	1·7	12·1	–22	3·1	5·0	3·7	11·8
6·8	11·8	5·0	23·6	23–27	7·0	12·4	6·0	25·4
6·5	10·1	4·2	20·8	28–32	7·7	9·3	7·0	24·0
4·5	9·4	3·7	17·6	33–37	4·3	8·4	3·6	16·3
1·9	7·2	2·3	11·4	38–42	2·0	6·1	2·6	10·7
3·1	7·1	4·3	14·5	43–	2·1	5·7	4·0	11·8
27·4	51·4	21·2	100·0	Total	26·2	46·9	26·9	100·0

In making a comparison between the males and females it is important that the two experiences should be comparable in regard to the number of patients discharged from year to year, the numbers included in each age group, and the physical condition on admission.

Of the 1,053 male patients 595 or 56·5 per cent. were under age 33 at the date of discharge, while of the 654 females 400 or 61·2 per cent. were of the same ages. It will be remembered that in Table I it was shown that the proportion of male to female patients discharged had been practically constant for the whole eight years; further, in Table II, that the same proportions of male and female persisted in each of the six age groups in which the data had been conveniently divided, while Table IV demonstrates that the clinical condition of the patients at admission was also similar for both sexes. Tables I, II, and IV show, therefore, that the data relative to each sex are in every way similarly constituted and therefore strictly comparable.

The bulk of the cases fall in Group 2, the percentage of males included therein being 51·4, and for the females 46·9. The distribution of the male and female patients among the three groups shows little variation; the only noticeable feature being a relatively slightly larger number of males in Groups 1 and 2 and a corresponding preponderance of females in Group 3. This small concentration of female patients in Group 3 occurs chiefly at the earlier ages at discharge; thus while 10·9 per cent. of the males are found in Group 3 at ages under 33, the corresponding percentage of females is 16·7;

the variation does not, however, appear to be of sufficient dimensions to warrant any particular weight being attached to it. A point to be noticed is that of the 1,707 patients no less than 751, or 44 per cent., were known to be dead on the anniversary of discharge in 1916. The significance of this is accentuated when it is further noted that the average number of years of life for which the 1,707 patients have been observed is almost exactly four, the total number of years of life observed since discharge being 6,819. If the males and females are considered separately the proportion dead will be seen to be 45 per cent. and 42 per cent. respectively.

In Tables 6, 7, and 8 (see Appendix A) are given the whole of the facts deduced from the after-histories of the 1,707 patients. For the purpose of easy reference the summaries of these tables are reproduced below in Table V.

TABLE V

Condition on Admission. All Groups.

Summary of Analysis

Group	Sex	No. of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected	Average No. of years of life observed
All	M. & F.	1707	6819	751	45·467	16·5	4·0
Groups	M	1053	4144	478	30·478	15·7	3·9
	F	654	2675	273	14·989	18·2	4·1
Group	M	289	1474	67	10·519	6·4	5·1
1	F	171	916	23	4·915	4·7	5·4
Group	M	541	2128	245	15·726	15·6	3·9
2	F	307	1220	131	6·899	19·0	4·0
Group	M	223	542	166	4·233	39·2	2·4
3	F	176	539	119	3·175	37·5	3·1

As already explained, it is proposed to make a comparison between the number of deaths which are known to have occurred and the number expected had the mortality rates of the general population been experienced. The rates of mortality, or the probabilities of dying within a year, at each age as deduced in the English Life Table No. 8, are given in Table 46, Appendix A; the rates are tabulated separately for male and female. Since the probability of dying within a year is substantially greater in the male section of the table, taking age for age, than in the female section, the female tuberculous patients may be expected to show slightly lower rates of mortality than the males. In order to give effect to this it will be correct to compare the male 'actual deaths' with those 'expected' by the male section of the life table, and to calculate the female 'expected deaths' from the female section. By so doing, the male experience may readily be compared with that of the females. In calculating the 'expected' deaths the rates of mortality proper to the particular sex have been used throughout.

The comparison between the 'actual' and 'expected deaths' is made under Table V in the last column but one, under the heading 'ratio

of actual to expected'. It may be pointed out that the whole of the 1,707 patients are here considered, but that in the case of some of them tubercle bacilli were not demonstrated in the sputum. The presence of T. B. in the sputum is of considerable significance and forms the subject of a separate investigation in Chapter V.

A study of Table V discloses the following general results:

(1) Taking all cases of both sexes together, for every death that would have occurred were the lives representative of the general population, there were 16·5 actual deaths among the sanatorium patients, the ratios for males and females being respectively 15·7 and 18·2. The ratio for the females being higher than that for the males is probably due to the fact already alluded to, that the female patients comprised a larger proportion of Group 3 cases.

(2) If reference be made to Group 1 patients only, it will be seen that the ratios are materially reduced; the males show 6·4 and the females 4·7. The difference between these two ratios is slight, and possibly due to the fact that of the female cases in this group 45·6 per cent. were T. B. —[1] on admission and discharge, while the corresponding figure for the males is only 22·5. The average number of years of life contributed by the patients in Group 1 is 5·2, which is over a year more than the average for the three groups taken together; this increase is considerable having regard to the fact that the maximum number of years of exposure for any life is nine years, and then only for those discharged in 1907.

(3) Group 2 patients, who are about equal in number to Groups 1 and 3 combined, show results which approximate closely to those already noted for the general body of patients. This is not unexpected. In this group the ratio for the males is 15·6 as compared with 19·0 for the females. Here also the female experience includes a larger percentage of T. B. — cases, but not to anything like the same extent as in Group 1. If it be remembered that as the ratios increase the less significant do any variations become there will be little inclination to attach much weight to the difference between the experience of the males and females in this group.

(4) The males and females in Group 3 give almost identical results, viz. 39·2 and 37·5 respectively. Thus these Group 3 patients show six times as many deaths as patients in Group 1, and more than twice as many as those in Group 2 for each death expected by the mortality rates of the general population table.

Attention may now be directed to the ratios of 'actual deaths' to 'expected' for each age group. Excess mortality has been shown to exist no matter what the relative condition on admission may have been; it will be interesting to see if this heavy mortality

[1] Cases in which T.B. were not demonstrated in the sputum are referred to as 'T.B. — cases'.

is experienced by patients without distinction as regards age, or whether some groups of ages present more favourable results than others. In Table VI are tabulated the ratios for each group of ages relative to each clinical group indicated by the condition on admission. As previously explained the age groupings refer to the ages at discharge.

TABLE VI

Condition on Admission. All Groups.

Ratios of Actual Deaths to Expected Deaths (E. L. No. 8)

According to Age at Discharge

Age	Group 1		Group 2		Group 3		All Groups	
Group	Male	Female	Male	Female	Male	Female	Male	Female
-22	14·9	5·4	27·1	41·9	71·4	102·0	25·8	40·2
23-27	9·7	7·0	25·4	33·2	86·1	53·8	26·3	28·1
28-32	10·0	5·3	22·1	24·6	49·4	42·6	20·8	20·4
33-37	7·6	4·0	14·6	15·0	46·2	44·9	16·0	15·6
38-42	3·0	7·8	16·9	13·9	41·9	41·7	16·4	16·6
43-	0·9	o 14[1]	6·4	6·2	17·0	13·1	6·5	6·8
Total	6·4	4·7	15·6	19·0	39·2	37·5	15·7	18·2

Apart from accidental fluctuations, the above table shows that the ratios are much higher at the younger ages. With one exception the figures for the first two age groups, namely ' up to 22 ' and ' 23–27 ', are the highest throughout. The exception occurs in the case of the females of Group 1, where the ratio for ages ' 38–42 ' rises slightly beyond those for the other ages of that group. In Group 1, the ratios for neither the males nor females show such steady reduction with the increase in age; this is probably due more to the comparatively low rate of mortality prevailing throughout the group than to the paucity of the data observed. The similarity of the experience of the males and females in each age group is very marked for ' All Groups ' taken together; the same feature is also noticeable for the groups considered separately, more especially in Groups 2 and 3.

This decline in the numerical value of the ratios does not mean that the rate of mortality is decreasing with advancing age, since when comparing the ' actual deaths ' with those ' expected ', account has automatically been taken of the natural increment in normal mortality which arises with the increase in age. As a matter of fact, the rate of mortality of these patients does not appear sensibly to vary as between the six age groups, and a reference to Table 6 (Appendix A) shows that for practical purposes it may be considered almost constant. That the rate of mortality of these lives who have contracted tuberculosis, and who have received treatment at a sanatorium, should be found to be approximately constant, and independent of the age of attack, at least between the limits of ages 20 to 50, is a point worthy of notice. Significance attaches to it when it is remembered, as can be seen from Table 46, that the rate of

[1] 14 cases discharged, no deaths.

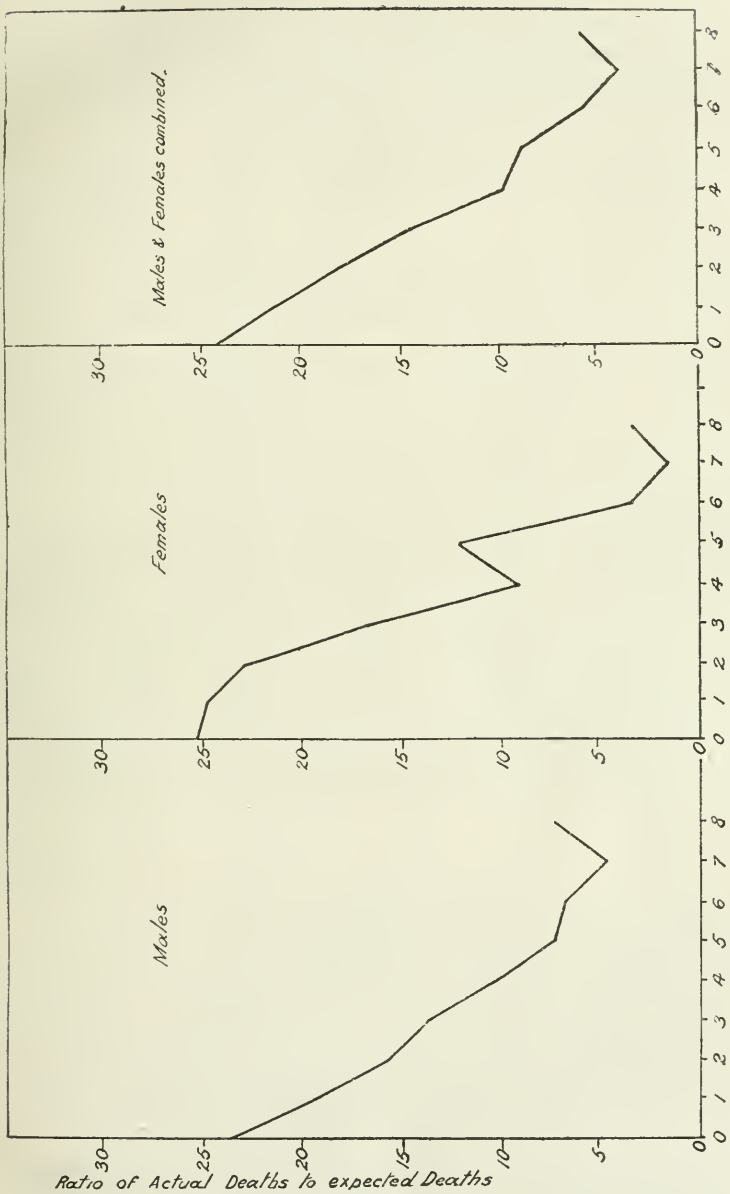

Diagram 2. Rates of Actual Deaths to Expected Deaths determined according to number of years elapsed since discharge (all groups).

mortality of the general population increases with age; the rate for age 50 is more than treble that at age 20. Whether the contraction of tuberculosis does to some extent immunize a sufferer from the attacks of other diseases it is not possible to say, although the current opinion is that it does not. But on the assumption that tuberculous persons are equally liable to the various diseases that afflict the population generally, it would seem, since as regards lives

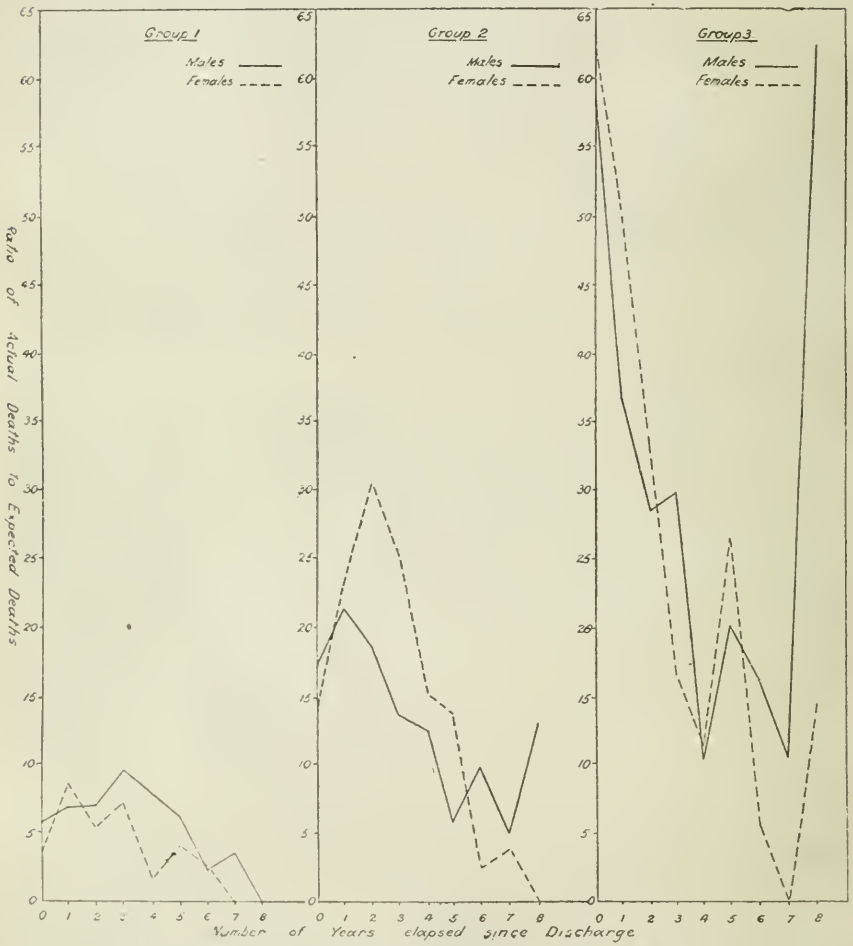

Diagram 3. Ratio of Actual Deaths to Expected Deaths determined according to number of years elapsed since discharge.

of the class here observed the excess mortality has been shown to be heavier at the younger ages, that tuberculosis occurring at about age 45 does not make for such a large increase in the mortality rate as when the onset occurs below age 25.

Turning now to Tables 3, 4 and 5, in which the whole of the data are set out in years elapsed since discharge, each of the six age groups having been combined, some idea may be gathered

as to the future of patients, year by year, after leaving the sanatorium. Speaking generally, the excess mortality is at its maximum during the first two or three years, after which it rapidly subsides, and in the case of Group 1 patients promises to disappear altogether after about ten years. Diagrams 2 and 3 show in graphical form the progression of this excess mortality for each of the nine years elapsed since discharge.

In studying these graphs it should be remembered that variations in unexpected directions will always occur when the number of observations upon which they are based is small. Were the data several times as extensive the accidental fluctuations would probably disappear.

Having this in mind, the manner in which the graphs for the female cases follow those for the male is striking. In diagram 2 the two graphs, for male and female separately, are similar in general outline, but combined, the descent in the value of the ratios for each year elapsed is seen to be steady and uninterrupted. Diagram 3 exhibits the ratios for each of the three groups taken separately, and the same features are in evidence. The variation in the later years for each group, the last group in particular, is due entirely to the paucity of the data there available; one death more or less being sufficient to introduce an exceptional bend in the graph. The examination of these diagrams confirms, what has been previously only surmised, that the critical period for a patient is during the first two or three years after discharge from the sanatorium. Among cases in Group 1 it will be noted that there is an inclination for the ratios to increase during these years and subsequently to decrease. The most probable explanation may be that a certain number of these cases, although diagnosed in an early stage, were not amenable to treatment and relapsed comparatively soon after discharge. The diagrams suggest that the probability of a relapse diminishes rapidly with every year during which good health is enjoyed.

It is of interest to determine how far the general results obtained at Midhurst are confirmed by the experience of patients treated elsewhere. The only available data which have been collected, tabulated, and analysed on an actuarial basis, and which are of sufficient extent to warrant special weight being attached to them, are those relating to the Adirondack Cottage Sanitarium, United States of America. The particulars of the patients who received treatment in this institution, published in the first instance by Dr. Lawrason Brown, have been analysed in accordance with actuarial principles by Messrs. Elderton and Perry.[1] The patients were drawn mainly from the north-eastern States: from the State

[1] A Fourth Study of the Statistics of Pulmonary Tuberculosis; the Mortality of the Tuberculous; Sanatorium and Tuberculin treatment. Based on Dr. Lawrason Brown's Adirondack Sanitarium data. W. P. Elderton and S. J. Perry. Published by Dulean & Co., London, 1913.

of New York in particular. Many nationalities were represented, but the Americans predominated; there were few, if any, coloured people.

Socially, the patients were drawn largely from the middle and upper middle classes. On the whole, they would appear to have enjoyed a somewhat higher social standing than those treated at Midhurst; for example, some of them were sufficiently well off to settle at Adirondack, and to constitute a small colony. Some reflection of this fact is to be expected in their subsequent mortality rates.

The Adirondack experience relates to the years 1885–1911, and has reference to 3,000 cases. It is divided into three parts, relating respectively to the first thousand cases from 1885 to 1897, the second thousand from 1898 to 1903, and the third thousand from 1904 to 1909. As, however, the data relating to the early years were defective in important particulars, the first 750 cases were excluded in a portion of the investigation, and it is with the remaining 2,250 cases, termed the Adirondack 'Special', that the Midhurst experience is here compared. In the Midhurst experience, observation could not in the case of any patient exceed nine years, and since, as has already been shown, the excess mortality is a function of the number of years elapsed since discharge, the Adirondack experience has been truncated so as to exclude the observations of any particular after-history beyond a period of nine years.

It will be remembered that in calculating the 'expected deaths', the English Life Table No. 8 was used for the Midhurst experience. Elderton and Perry, however, used the English Life Table No. 6; Tables Nos. 7 and 8 had not then been constructed. The English Life Table No. 6 was based on the two censuses taken in 1891 and 1901 respectively, and on the deaths of the decennial period included by those years. Table No. 8 is the latest English population mortality table now available, and is based upon facts contemporary with the years during which the Midhurst patients have been observed. But as this table shows substantially lower rates of mortality than No. 6 it will not be strictly correct to compare the ratios of the Adirondack deaths to the 'expected' by No. 6 with the ratios of Midhurst deaths to the 'expected' by No. 8. In order that a proper comparison should be made, the Midhurst expected deaths have been re-calculated by Table No. 6, and entirely fresh ratios obtained on this basis.

Before making any comparisons the following points may be noted:

(1) The results relating to the Adirondack Sanitarium are tabulated according to the number of years elapsed since admission; the observations in years 0 and 1, at least, include the period in which the patients were actually undergoing treatment. The Midhurst experience, however, relates only to after-histories subsequent to discharge.

(2) Owing to the method of construction employed, the results tabulated for year 0 in the Adirondack experience have reference to only one half-year's observation: for Midhurst each successive duration indicates a full year of exposure.

(3) The average period of stay at Midhurst, as previously stated, was between four and five months; at Adirondack the average time devoted to treatment at the Sanitarium was probably much in excess of this.

(4) The patients at Adirondack, as in the case of those at Midhurst, were on admission divided into three groups, i.e. 'incipient', 'advanced', and 'far advanced', in accordance with the method of classification employed in this Report: this facilitates the comparison of the two experiences. It must, however, be pointed out that the proportions of patients included in the various groups are not the same for the two institutions. This is seen from Table VII. All these points should be borne in mind when comparing the two experiences.

Table VII

Number of Patients Admitted and Discharged at Adirondack and Midhurst respectively for each Sex and Group.

	Males				Females			
	Group 1	Group 2	Group 3	All Groups	Group 1	Group 2	Group 3	All Groups
Numbers at								
Adirondack	386	665	61	1112	395	603	44	1042
at Midhurst	289	541	223	1053	171	307	176	654
Percentages at								
Adirondack	34·7	59·8	5·5	100·0	37·9	57·9	4·2	100·0
at Midhurst	27·4	51·4	21·2	100·0	26·2	46·9	26·9	100·0

In Tables VIII, IX, and X, all ages at entry have been combined; and the nine years over which the observations extend are divided into three periods, i.e. durations (0–2), (3–5), and (6–8) years.

Table VIII

Mortality from Date of Admission.

Adirondack (Special). Expected Deaths by E. L. No. 6

Class	Number of Years since Admission									
	0–2			3–5			6–8			0–8
	Actual Deaths	Expected Deaths	Ratio	Actual Deaths	Expected Deaths	Ratio	Actual Deaths	Expected Deaths	Ratio	Ratio
Group 1										
Males	21	6.07	3.5	25	5.79	4.3	12	3.48	3.4	3.8
Females	11	5.78	1.9	19	5.48	3.5	5	3.31	1.5	2.4
Group 2										
Males	125	11.51	10.9	107	8.96	11.9	32	4.66	6.9	10.5
Females	103	8.71	11.8	88	6.98	12.6	31	4.30	7.2	11.1
Group 3										
Males	44	.96	45.8	6	.25	24.0	2	.15	13.3	38.2
Females	28	.59	47.5	10	.23	43.5	1	.04	25.0	45.3
All Gronps										
Males	190	18.54	10.2	138	15.00	9.2	46	8.29	5.5	8.9
Females	142	15.08	9.4	117	12.69	9.2	37	7.65	4.8	8.4
M. & F.	332	33.62	9.9	255	27.69	9.2	83	15.94	5.2	8.7

Table IX

Mortality from Date of Discharge.

Midhurst. Expected Deaths by E. L. No. 8

Class	Number of Years since Discharge									
	0–2			3–5			6–8			0–8
	Actual Deaths	Expected Deaths	Ratio	Actual Deaths	Expected Deaths	Ratio	Actual Deaths	Expected Deaths	Ratio	Ratio
Group 1										
Males	33	5.083	6.5	30	3.720	8.1	4	1.716	2.3	6.4
Females	14	2.353	5.9	8	1.811	4.4	1	.751	1.3	4.7
Group 2										
Males	178	9.335	19.1	52	4.642	11.2	15	1.749	8.6	15.6
Females	91	4.155	21.9	38	1.999	19.0	2	.745	2.7	19.
Group 3										
Males	143	3.103	46.1	19	.897	21.2	4	.233	17.2	39.2
Females	103	1.992	51.7	14	.796	17.6	2	.387	5.2	37.5
All Groups										
Males	354	17.521	20.2	101	9.259	10.9	23	3.698	6.2	15.7
Females	208	8.500	24.5	60	4.606	13.0	5	1.883	2.7	18.2
M. & F.	562	26.021	21.6	161	13.865	11.6	28	5.581	5.0	16.5

Table X

Mortality from Date of Discharge.

Midhurst. Expected Deaths by E. L. No. 6

Class	Number of Years since Discharge									
	0–2			3–5			6–8			0–8
	Actual Deaths	Expected Deaths	Ratio	Actual Deaths	Expected Deaths	Ratio	Actual Deaths	Expected Deaths	Ratio	Ratio
Group 1										
Males	33	7·000	4·7	30	5·082	5·9	4	2·297	1·7	4·7
Females	14	3·423	4·1	8	2·612	3·1	1	1·077	·9	3·2
Group 2										
Males	178	12·886	13·8	52	6·324	8·2	15	2·373	6·3	11·4
Females	91	6·011	15·1	38	2·849	13·3	2	1·046	1·9	13·2
Group 3										
Males	143	4·249	33·7	19	1·201	15·8	4	·312	12·8	28·8
Females	103	2·849	36·2	14	1·116	12·5	2	·524	3·8	26·5
All Groups										
Males	354	24·135	14·7	101	12·607	8·0	23	4·982	4·6	11·5
Females	208	12·283	16·9	60	6·577	9·1	5	2·647	1·9	12·7
M. & F.	562	36·418	15·4	161	19·184	8·4	28	7·629	3·7	11·9

A comparison of Table IX with Table X, both of which relate to Midhurst, shows the variation in the results obtained by using the English Life Table No. 8 instead of the English Life Table No. 6: taking all groups and durations together the ratios in Table IX are about 40 per cent. greater than those in Table X. For the purpose of comparing the two experiences the advisability of calculating the 'expected deaths' for each institution from the same table of mortality is therefore clearly demonstrated.

Comparing Tables VIII and X, it will be noticed that the Adirondack results appear to be the more favourable. The difference, it is suggested, is more apparent than real, since the Midhurst experience contains a much larger percentage of Group 3 cases than that of Adirondack.

Taking Groups 1, 2, and 3 separately, Adirondack shows to a little advantage for the first two groups, but not so for Group 3. It will be seen that in Group 3 the Midhurst ratios are the smaller throughout for the total for each sex and for each of the three periods elapsed since observations commenced.

Dealing with the durations since discharge it will be noted that these remarks are also applicable to the first period (0–2) years. This may in part be accounted for by the patients to whom these records refer having been under treatment in the sanatorium during the major portion of the first year. For the period (3–5) years there is little difference between the ratios; but for the period (6–8) years the Midhurst results are positively the better.

It has been already pointed out that at Midhurst Group 1 for females includes a much larger percentage of T. B. – cases than the corresponding group for males: this was suggested as a reason

why the female mortality in this group appeared to be lighter. The same feature is noticeable in the Adirondack data, and in that experience also the females include a larger percentage of T. B. — cases, the figures being 44·6 per cent. for males and 61·8 per cent. for females. This important fact, common to both experiences, coupled with the probability that women are better able than men to continue treatment after their discharge from a sanatorium, may be the cause of the lighter mortality shown by female patients in Group 1.

An inquiry was made into the age distribution of the cases at the American Sanitarium. It would appear that the average age of the cases at Adirondack was lower than that at Midhurst, the proportion of patients above age 32 at the former being much less than at the latter. Since the mortality has been shown to be relatively worse at the younger ages both at Midhurst and at Adirondack, it would seem that in the comparison between the two institutions the Adirondack results would suffer to that extent.

To complete the comparison, taking into account all the various points of similarity and divergence between the two experiences, it is thought that the results at Adirondack may, on the whole, be said to be slightly the more favourable, but not more so than was to be expected having regard to the slightly better social class from which the patients for that institution were drawn. Generally speaking, it is remarkable how often and how closely the two sets of figures confirm each other. Some of the most well-marked features disclosed in the Midhurst investigation, such as the effect of age, duration since treatment, clinical condition, &c., on mortality rates, are faithfully reproduced in the study of the Adirondack experience.

The characteristics resulting from the general analysis may now be summarized as under :

(1) That the separation of the males from the females leading to the division of the data into two sections, one twice the size of the other, shows that the results for the male section are confirmed practically throughout by those for the female section.

(2) That the mortality experienced is very heavy ; the mortality rates for Group 1 patients are nearly six times, for Group 2 patients over sixteen times, and for Group 3 patients about thirty-eight times greater than the rates appertaining to the population of England and Wales.

(3) That the mortality is relatively more excessive at the younger ages at discharge.

(4) That the critical period for patients, especially those in Groups 1 and 2, is during the first two or three years following discharge ; subsequently, the excess mortality is materially reduced ; in fact, for Group 1, the rates for durations (6–8) years are not seriously above the normal.

(5) That the results obtained at Midhurst are generally similar, in respect of important features, to those disclosed in Elderton and Perry's Adirondack investigation; this agreement of results arrived at by independent observers from an examination of two sets of data is significant and adds weight to the conclusions detailed in this Report.

The Results in Relation to the Value of Sanatorium Treatment.

It is not easy to estimate the usefulness of sanatoriums as a means of curing pulmonary tuberculosis from the experience of the Midhurst patients, since there exist no data of a similar character upon which to determine the mortality rates of cases of consumption prevailing before the introduction of sanatorium methods, or at the present time, after treatment upon other principles. Physicians of long and intimate experience of the disease are unanimous in the opinion that the introduction of sanatorium methods has materially improved the outlook for the average consumptive, and that residence in a sanatorium represents the best treatment available at the present time. None the less, the records just given reveal pulmonary tuberculosis as a disease of the utmost gravity; and further, they show that residence in a sanatorium, much though it can accomplish in individual cases, is a means of treatment which is far from being adequate. Something more is needed. Treatment in a sanatorium should be followed by systematic after-care, by which the principles underlying the hygienic cure of tuberculosis are embodied in the everyday life of the patient on his return home. Under these conditions only is it probable that the benefit derived from sanatorium treatment will prove lasting in character.

CHAPTER II

Mortality Experience determined according to the Condition on Discharge.

So far, the experience has been considered in relation to the condition on admission. It is now proposed to carry the analysis a step further and to investigate the mortality rates of the various groups of cases classified in accordance with the condition on discharge.

A priori, it would seem probable that patients classed on admission in Group 1 and discharged 'ARRESTED' would have a more favourable prognosis than those who, though classed in the same group on admission, were discharged 'UNIMPROVED'; but can it be said with equal readiness that Group 1 patients who are discharged 'WORSE' enjoy a more favourable prospect of longevity than patients in Group 3 discharged 'MUCH IMPROVED'?

To detail the modifications in the rates of mortality resulting from a consideration of the condition after, as well as that existing before treatment, is therefore the immediate object in view.

On discharge from the sanatorium, the patients were classified into four groups according to their clinical condition at that date. The four groups are styled 'ARRESTED', 'MUCH IMPROVED', 'IMPROVED', and 'WORSE'; it was considered unnecessary to make any distinction between those in whom no improvement was apparent and those whose condition definitely deteriorated.

The definition of the terms 'ARRESTED', 'MUCH IMPROVED', &c. has already been given (page 8).

TABLE XI

Number of Male Patients 1,053.

Age Group	Number in Group 1 on Admission 289				Number in Group 2 on Admission 541				Number in Group 3 on Admission 223				Total All Groups 1053			
	Condition on Discharge				Condition on Discharge				Condition on Discharge				Condition on Discharge			
	a	b	c	d	a	b	c	d	a	b	c	d	a	b	c	d
-22	26	15	2	5	12	25	9	15	1	4	6	7	39	44	17	27
23-27	47	23	2		28	52	24	20		10	25	18	75	85	51	38
28-32	39	22	5	3	20	50	18	18		16	11	17	59	88	34	38
33-37	26	20		1	19	66	6	8	1	9	11	18	46	95	17	27
38-42	10	9		1	10	41	12	13		3	9	12	20	53	21	26
43-	13	18	1	1	15	36	16	8		15	17	13	28	69	34	22
Total	161	107	10	11	104	270	85	82	2	57	79	85	267	434	174	178
	Percentages				Percentages				Percentages				Percentages			
	a	b	c	d	a	b	c	d	a	b	c	d	a	b	c	d
-22	9·0	5·2	·7	1·8	2·2	4·6	1·7	2·8	·4	1·8	2·7	3·2	3·7	4·2	1·6	2·6
23-27	16·2	8·0	·7		5·2	9·6	4·4	3·7		4·5	11·2	8·1	7·1	8·1	4·9	3·6
28-32	13·5	7·6	1·8	1·1	3·7	9·2	3·3	3·3		7·2	4·9	7·6	5·6	8·4	3·2	3·6
33-37	9·0	6·9		·3	3·5	12·2	1·1	1·5	·4	4·1	4·9	8·1	4·4	9·0	1·6	2·6
38-42	3·5	3·1		·3	1·8	7·6	2·2	2·4		1·3	4·1	5·4	1·9	5·0	2·0	2·4
43-	4·5	6·2	·3	·3	2·8	6·7	3·0	1·5		6·7	7·6	5·8	2·7	6·5	3·2	2·1
	55·7	37·0	3·5	3·8	19·2	49·9	15·7	15·2	·8	25·6	35·4	38·2	25·4	41·2	16·5	16·9

Table XII

Number of Female Patients 654.

Age Group	Number in Group 1 on Admission 171 — Condition on Discharge				Number in Group 2 on Admission 307 — Condition on Discharge				Number in Group 3 on Admission 176 — Condition on Discharge				Total All Groups 654 — Condition on Discharge			
	a	b	c	d	a	b	c	d	a	b	c	d	a	b	c	d
-22	16	3		1	8	12	7	6	1	2	14	7	25	17	21	14
23-27	32	12	1	1	15	32	23	11	1	7	16	15	48	51	40	27
28-32	35	11	2	2	7	26	14	14		12	19	15	42	49	35	31
33-37	20	7	1		11	25	12	7		4	11	9	31	36	24	16
38-42	8	2	2	1	6	17	11	6		5	4	8	14	24	17	15
43-	11	2		1	8	14	8	7	2	5	11	8	21	21	19	16
Total	122	37	6	6	55	126	75	51	4	35	75	62	181	198	156	119
	Percentages				Percentages				Percentages				Percentages			
	a	b	c	d	a	b	c	d	a	b	c	d	a	b	c	d
-22	9·3	1·7		·6	2·6	3·9	2·3	1·9	·6	1·1	8.	3·9	3·8	2·6	3·2	2·1
23-27	18·7	7·0	·6	·6	4·9	10·4	7·5	3·6	·6	3·9	9·1	8·5	7·3	7·8	6·1	4·1
28-32	20·4	6·4	1·2	1·2	2·3	8·5	4·6	4·6		6·8	10·8	8·5	6·4	7·5	5·4	4·7
33-37	11·7	4·1	·6		3·6	8·1	3·9	2·3		2·3	6·2	5·1	4·8	5·5	3·7	2·5
38-42	4·7	1·2	1·2	·6	1·9	5·5	3·6	1·9		2·9	2·3	4·6	2·1	3·7	2·6	2·3
43-	6·4	1·2		·6	2·6	4·6	2·6	2·3	1·1	2·9	6·2	4·6	3·2	3·2	2·9	2·5
Total	71·2	21·6	3·6	3·6	17·9	41·0	24·5	16·6	2·3	19·9	42·6	35·2	27·6	30·3	23·9	18·2

The manner in which the patients are distributed among the four groups is much the same for both sexes; here and there slight differences may be observed, the effect of which on general mortality rates will be noted, but no wide divergence in incidence is apparent.

Taking all groups together the percentage of male and female patients discharged are respectively 25 and 28 'ARRESTED', 41 and 30 'MUCH IMPROVED', 17 and 24 'IMPROVED', and 17 and 18 'WORSE'; the females, as compared with the males, thus include a larger proportion of cases discharged 'IMPROVED', while the males have a nearly similar preponderance of cases which reached the 'MUCH IMPROVED' condition.

As would be hoped, if not expected, the majority of the patients admitted in Group 1 are discharged either 'ARRESTED' or 'MUCH IMPROVED': these two classifications include about 93 per cent. of the patients in each sex. About 56 per cent of the males gave signs consistent with 'ARRESTED' disease and 37 per cent. were 'MUCH IMPROVED'; the corresponding figures for the females are 71 and 22 per cent. respectively. These differences in proportions are probably due to the fact previously pointed out that the females include a much larger proportion of cases in which T. B. were not found in the sputum, and in which therefore arrest of the disease was more likely to result from treatment.

Group 2 does not contain so large a percentage of 'ARRESTS', the

patients discharged in a 'MUCH IMPROVED' condition predominating; the remainder of patients in this group are fairly evenly distributed among those 'ARRESTED', 'IMPROVED', or 'WORSE'. As between the sexes the males appear to advantage, since the relative number discharged 'MUCH IMPROVED' is greater; the excess over the females being about 9 per cent. Of the females nearly 25 per cent. were 'IMPROVED' after treatment: this it may be noted is about 9 per cent. greater than the percentage given for the corresponding section of males.

Of 399 Group 3 patients, only six, two males and four females, were discharged 'ARRESTED', while about 75 per cent. of them were classified as 'IMPROVED' or 'WORSE'. As in Group 2, so in Group 3 there is among the males a larger percentage of 'MUCH IMPROVED' cases than among the females; the excess is about 6 per cent., which in turn approximately represents the difference between the male and female 'IMPROVED' cases, the difference here being in favour of the latter.

Except in Group 1 the percentage of patients who were discharged with disease 'ARRESTED' is nearly the same for both sexes.

The mortality rates convey a fair impression as to the degree to which a prognosis made on admission may be modified at discharge according to the relative response patients have made to treatment. The cases are fully analysed in Tables 9–16 (Appendix A); complete information is there given as to the number of years of life observed, the number of 'actual deaths' and 'expected deaths', as well as the ratios of the former to the latter. The ratios of the 'actual deaths' to those 'expected' are, however, reproduced below in Table XIII.

TABLE XIII

Ratios of Actual Deaths to Expected Deaths, tabulated according to Condition on Admission and Discharge.

Males

Condition on Discharge	Group 1	Group 2	Group 3	All Groups
Arrested	3·9	5·3	0·2)[1]	4·4
Much Improved	7·1	12·5	15·2	11·3
Improved	43·8	23·4	47·6	33·1
Worse	35·4	51·4	74·8	59·5

Females

Condition on Discharge	Group 1	Group 2	Group 3	All Groups
Arrested	3·4	5·8	6·6	4·2
Much Improved	7·8	14·2	17·8	13·8
Improved	14·8	27·4	30·0	28·2
Worse	10·6	57·4	102·9	68·5

The first point to be noticed is the similarity in the ratios showing separately the experience of the two sexes. Perhaps this will be better seen by means of a diagram in which the ratios are set out in graphical fashion.

[1] Two discharged, no deaths.

The relative heavy mortality as shown by the high ratio experienced by the males in Group 1 classified as 'IMPROVED' is possibly due to the small number of patients there observed, rather than to probable experience; little emphasis, if any, should

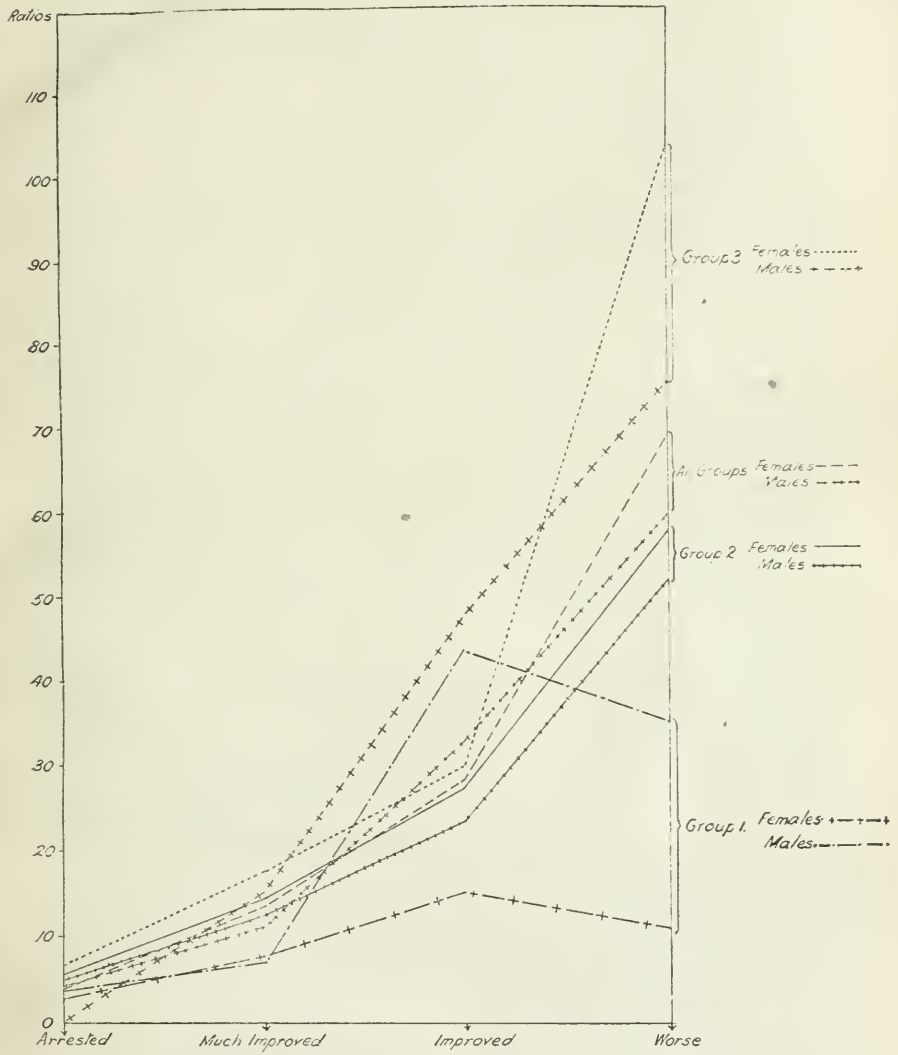

Diagram 4. Ratio of Actual Deaths to Expected Deaths determined according to condition on discharge.

be laid on the fact that these ratios are higher than those for Group 2. This abnormality is not in evidence in the female section of Group 1, where the ratio appears more nearly to approximate to that which would be expected; females in this group

discharged 'WORSE' show a ratio which is lower than might be anticipated.

Reading Table XIII vertically and taking all groups at admission together, both sexes being combined, the ratios are for the 'ARRESTED' approximately 4, 'MUCH IMPROVED' 12, 'IMPROVED' 31, and 'WORSE' a little over 60. Group 1 shows better results throughout; in Group 3 mortality is very heavy, while the figures of Group 2 reflect the general experience of all the groups combined.

It will be remembered that in Chapter I, when giving the mortality rates with reference only to the condition on admission, attention was drawn to the lower ratio shown in Group 1 by the female patients. It was then suggested that this was due to the larger percentage of T. B. — cases included in the female section. Some confirmation of this is now revealed, since the female cases in Group 1 include a high proportion of cases discharged 'ARRESTED', a condition which by definition presupposes the sputum to be negative either on admission or discharge, or both. Females in Group 1 include 71 per cent. of 'ARRESTS' with a mortality ratio of 3·4, and 22 per cent. 'MUCH IMPROVED' with a ratio of 7·8: the males in the same group include only 56 per cent. of 'ARRESTS' with a mortality ratio of 3·9, but 37 per cent. 'MUCH IMPROVED' with a ratio of 7·1. The 'ARRESTED' and 'MUCH IMPROVED' constitute in the case of each sex about 93 per cent. of the total discharges, and about one-half of the superiority of the females in Group 1 taken as a whole is attributable to the larger percentage of cases discharged in an arrested condition. The other half is due to the comparatively poor results shown by the males in Group 1 for conditions 'IMPROVED' and 'WORSE' to which notice has already been directed.

Although the ratios for Group 2 for each condition on discharge are higher for the females than for the males a similar line of argument may even be pursued in regard to this group. The proportion of 'ARRESTS' and 'WORSE' for male and female are approximately the same, but as the male section includes a larger proportion of 'MUCH IMPROVED' cases and a correspondingly smaller proportion of 'IMPROVED' cases than the female section, the males in Group 2 as a whole should show slightly lighter mortality rates. If reference be made back to Chapter I it will be seen that this is so: the ratios being 15·6 for males and 19·0 for females. Practically the whole of the difference between the ratios for the two sexes of 3·4 may be ascribed to the variation in the incidence of the groupings on discharge.

Reading Table XIII horizontally, it will be noticed that if a patient be discharged 'ARRESTED', the subsequent mortality is not very different for Groups 1, 2, and 3; this suggests that providing arrest of the disease be obtained, the extent of the disease is not of such importance as would be the case were the condition on discharge less favourable. Group 1 would be expected to give the best results, and in fact does so; but in no case, irrespective of condition on admission, where the patient has been discharged 'ARRESTED' does the ratio exceed 7·0. The 'MUCH IMPROVED' patients do not present such favourable results as those 'ARRESTED', and

show comparatively high mortality; there are also larger differences between the ratios for the three groups. The 'IMPROVED' results are still less favourable. Those discharged 'WORSE' give the poorest results of all, the mortality being painfully heavy. In this connexion it is of interest to note that not only is the mortality heavy, but of the patients admitted in Group 3 and discharged in a worse condition, approximately two-thirds of the recorded deaths occur within a year of discharge.

TABLE XIV

Patients admitted in Group 3 and Discharged 'WORSE'.

Sex	Number of			Percentage of		
	Patients Discharged	Deaths Recorded	Recorded Deaths in 1st year	Patients Discharged whose Deaths are Recorded	Deaths Recorded in 1st year	Deaths in 1st year to total Deaths
Males	85	72	48	84·7	56·5	66·7
Females	62	53	35	85·5	56·5	66·0
Males & Females	147	125	83	85·0	56·5	66·4

Thus of 147 male and female patients 85·0 per cent. died during the period of observation, 56·5 per cent. died in the first year, and of the deaths only 33·6 per cent. lived a year beyond the date of discharge. The male and female experiences in this respect are nearly identical.

The importance of securing arrest of the disease may be seen by comparing the ratios given in Table XIII for the 'ARRESTED' cases 'All Groups' with the ratios shown in Table VI for Group 1. In the case of both sexes the ratios for the cases discharged 'ARRESTED' are slightly smaller than those for Group 1, although, in addition to a few patients of Group 3, 36 per cent. of the cases included in the former category were admitted in Group 2. Even the patients discharged 'MUCH IMPROVED' appear to show better results than those of Group 2, although of the 'MUCH IMPROVED' cases 23 per cent. are from Group 1, 63 per cent. from Group 2, and 14 per cent. from Group 3.

The condition on discharge from a sanatorium is thus seen to be of great moment. The results just given suggest that so long as the patient, irrespective of his condition on admission, is making satisfactory progress, every encouragement and facility should be offered to extend the period of treatment, so that even if 'ARREST' of the disease is improbable, except with prolonged treatment, the greatest improvement possible should be attained before he is discharged, in the hope that 'ARREST' may follow as the result of after-care. The more residence in a sanatorium is prolonged, while further improvement is possible, the greater will be the economic return for the money and time thus expended.

Attention has already been called to the fact that the mortality is comparatively heavier at the younger ages at discharge. No variation of this is apparent when the data are rearranged and tabulated solely in reference to the condition after treatment.

Table XV

Ratio of Actual Deaths to Expected Deaths in each Age Group according to the Condition on Discharge.

Age Group	Males				Females			
	Arrested	Much Improved	Improved	Worse	Arrested	Much Improved	Improved	Worse
-22	7·5	23·1	71·9	63·9	6·3	39·1	87·8	96·5
23-27	7·2	20·3	51·9	96·3	7·8	21·5	42·2	120·7
28-32	4·0	16·1	54·0	72·3	5·1	14·1	25·9	98·9
33-37	5·2	12·9	43·7	75·9	2·9	16·3	22·5	59·1
38-42	3·0	12·1	29·3	48·9	3·2	12·1	30·5	47·2
43-	1·6	4·2	13·7	28·2	1·6	3·4	10·2	28·8
Total	4·4	11·3	33·1	59·5	4·2	13·8	28·2	68·5

The extent to which the figures in Table XV for each sex separately confirm one another is marked throughout.

It is interesting to calculate the average number of years of life contributed by the cases included in the four groupings.

Table XVI

The Average Number of Years of Exposure included in Group indicating Condition on Discharge.

Condition on Discharge	Males			Females		
	Number of Patients	Years of Exposure	Average Number of years of Exposure	Number of Patients	Years of Exposure	Average Number of years of Exposure
Arrested	267	1391	5·2	181	993	5·5
Much Improved	434	1868	4·3	198	859	4·3
Improved	174	510	2·9	156	578	3·7
Worse	178	375	2·1	119	245	2·1

In regarding this table it should be remembered that the maximum number of years for which any patient discharged in 1907—the first year in which discharges took place—could have been observed is nine; for those discharged in subsequent years the number will be correspondingly reduced.

If the patients had been discharged in equal numbers in each year, every case having been retained under observation from the moment of discharge until the anniversary in 1916, none having died or been lost sight of, the average number of years of exposure for each patient would have been 5·5. As a matter of fact the discharges were distributed over the period in such a way that a few more were discharged in the earlier years, the actual maximum average exposure being 5·6 years. No attempt was

made to see whether the proportion of cases discharged in each of the four groupings was the same from year to year; indeed there is no reason to anticipate any marked disturbance in the incidence in the numbers so discharged. In view of the female 'ARRESTS' giving an average of 5·5 years although 32 or 18 per cent. died or were lost sight of, it is suggested that perhaps there may have been a slightly larger number who were discharged 'ARRESTED' in the first half of the period covered by the investigation. The differences in the average number of years of exposure shown in Table XVI in respect of the various conditions on discharge are, however, significant.

The heavy mortality rates to which these tuberculous patients are subject may be presented in another way. The average age at which the whole body of patients was exposed to risk is approximately 33. The rate of mortality experienced by the patients discharged 'ARRESTED' taking all ages together is 2·95 per cent., which is the rate of mortality shown by the population table for age 60.

Similarly for patients discharged 'MUCH IMPROVED', the rates of mortality approximate to that of the population table at ages 74 and upwards. These results are somewhat startling.

Viewing the mortality as a function of the number of years elapsed since discharge it will be observed from Table XVII that for the 'ARRESTED' cases it is comparatively low in the early years, but gradually increases until it reaches a maximum in the fourth year, from which point it decreases and approaches the normal in the seventh year. This would appear to be an exemplification of the survival of the fittest, involving the elimination during the early years of those in whom arrest of the disease has been temporary only. The 'MUCH IMPROVED' show higher ratios from the outset, and these rise to a maximum immediately after the first and second years, and then rapidly decrease: the ratios for the sixth, seventh, and eighth years are substantially better than those for the first year; the results of treatment, however, for the 'MUCH IMPROVED' would appear to be more transient than in the case of the 'ARRESTED'. The excess mortality for the 'MUCH IMPROVED' patients as shown in Table XVIII does not promise to disappear in the ninth year, and probably would not actually do so even if the observations were extended for a further term of years. It was not thought of sufficient interest to examine in this respect the experience of patients who became worse or only improved during treatment.

Table XVII

Arrested Cases tabulated according to Years elapsed since Discharge.

Years elapsed since Discharge	267 Males			181 Females			448 Males and Females		
	Actual Deaths	Expected Deaths	Ratio of Actual to Expected	Actual Deaths	Expected Deaths	Ratio of Actual to Expected	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
0	5	1·581	3·2	2	·891	2·2	7	2·472	2·8
1	4	1·602	2·5	5	·916	5·5	9	2·518	3·6
2	10	1·496	6·7	6	·855	7·0	16	2·351	6·8
3	11	1·347	8·2	4	·768	5·2	15	2·115	7·1
4	4	1·089	3·7		·679		4	1·768	2·3
5	3	·907	3·3	4	·574	7·0	7	1·481	4·7
6	2	·729	2·7	2	·441	4·5	4	1·170	3·4
7	2	·455	4·4		·253		2	·708	2·8
8		·210			·137			·347	
Total	41	9·416	4·4	23	5·514	4·2	64	14·930	4·3

Table XVIII

Much Improved Cases tabulated according to Years elapsed since Discharge.

Years elapsed since Discharge	434 Males			198 Females			632 Males and Females		
	Actual Deaths	Expected Deaths	Ratio of Actual to Expected	Actual Deaths	Expected Deaths	Ratio of Actual to Expected	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
0	29	2·929	9·9	10	·997	10·0	39	3·926	9·9
1	44	2·890	15·2	14	·977	14·3	58	3·867	15·0
2	28	2·259	12·4	15	·775	19·4	43	3·034	14·2
3	26	1·888	13·8	12	·629	19·1	38	2·517	15·1
4	18	1·634	11·0	9	·531	16·9	27	2·165	12·5
5	10	1·217	8·2	6	·391	15·3	16	1·608	10·0
6	8	·967	8·3	1	·294	3·4	9	1·261	7·1
7	1	·710	1·4	1	·216	4·6	2	·926	2·2
8	3	·307	9·8		·105		3	·412	7·3
Total	167	14·801	11·3	68	4·915	13·8	235	19·716	11·9

The analysis of the mortality rates experienced by patients discharged in the various conditions suggests the following observations:—

(1) That the Medical Officer is able to make a tolerably accurate prognosis on the basis of the condition on admission and the response made to treatment; the different mortality rates shown in each of the four groups and the similarity of the male and female results illustrate this point.

(2) That 'ARREST' of pulmonary tuberculosis associated with complete disappearance of all signs and symptoms of active disease does not imply a cure, although doubtless some 'ARRESTED' patients are fortunate enough ultimately to effect an actual cure. It is clearly demonstrated that cases

classified as 'ARRESTED', taken as a body, experience substantially higher mortality rates than those shown by the general population.

(3) That when the patient is discharged 'ARRESTED', the subsequent mortality is not greatly affected by the condition on admission to the sanatorium; but that if discharged in a condition described otherwise than 'ARRESTED' the condition at commencement of treatment influences considerably the prospects of longevity.

(4) That in making a prognosis the condition on discharge is at least of equal importance to that on admission: that is to say, patients in Group 3 at time of admission, but discharged 'MUCH IMPROVED', have on the average a more favourable prognosis than patients admitted in Group 2, and possibly also in Group 1, but discharged only 'IMPROVED' or 'WORSE'.

CHAPTER III

The Treatment of Pulmonary Tuberculosis with Tuberculin.

In view of the practical importance of the subject, this section has been written in some detail. The value of tuberculin in the treatment of pulmonary tuberculosis has been for some years, and still remains, a matter of controversy. Despite this fact, however, little attempt has been made in this country to submit the issue to a systematic and controlled investigation.

Scope of the Inquiry.

This inquiry records the experience of the use of tuberculin in the treatment of pulmonary tuberculosis during a period of rather more than three consecutive years, beginning October 1911.

The observations were made in the King Edward VII Sanatorium, which, in virtue of its position and equipment, enjoys exceptional facilities for the treatment of pulmonary tuberculosis.

The scope of the inquiry may be defined, therefore, as observations upon the effect of treatment with tuberculin, when given in addition to the hygienic measures generally practised in a sanatorium. This implies that the inoculations were given to patients who were living under particularly favourable conditions, and who were receiving efficient general treatment.

Selection of Patients.

Theoretically, every patient deemed capable of responding to the stimulus of tuberculin is suitable for this form of treatment. This principle was at first followed; thus the process of selection was one of elimination of the less fit; the chief contra-indications

recognized being evidence of actively extending disease, of constitutional deterioration, disorders of nutrition, or the existence of complications, such as renal disease, diabetes, &c. A history of haemoptysis or the presence of a slight degree of fever was not regarded as necessarily forbidding the use of tuberculin. This basis of selection is a wide one, and allows of tuberculin being given to patients suffering from various phases of the disease. For the most part, however, it was given to those patients, irrespective of the extent of the pulmonary lesion, who had reached a high level of convalescence as shown by absence of fever, unimpaired nutrition, and a general sense of well-being.

Variety of Tuberculin used.

The large number of tuberculin preparations now on the market are essentially identical in action; the difference between them being quantitative only. They all produce the characteristic specific reaction, and immunize against each other. During the work now under review, Albumose Free Old Tuberculin (A. F.) and Koch's Bacillary Emulsion (B. E.) were used almost exclusively.

Method of Administration adopted.

After careful consideration the method of administration practised by Bandelier and Roepke was adopted, the technique detailed in their text-book being closely followed. During 1914 the method of administration was modified, as the result of the experience that had been gained. It then approximated to the 'reactionless' method described by Sahli and Trudeau.[1] Bandelier and Roepke's principles may thus be summarized:—

The initial dose. In favourable cases ·00001 c.c.; in less favourable cases ·000001 c.c. In exceptionally favourable cases ·0001 c.c.

The maximum dose. As large an amount as possible, up to 1 c.c. of undiluted tuberculin.

Increase of dose. Approximately after the following scheme:— 0·1, 0·15, 0·2, 0·3, 0·5, 0·7 of each dilution.

Interval between the doses. With the higher dilutions, an interval of two or three days, gradually increasing with the lower dilutions to an interval of seven days or more. The intervals can only be stated approximately; both the increase of the dose and the interval between the doses depend upon the nature of the response to the last inoculation.

[1] The details as to the administration of tuberculin to the 238 tuberculin treated cases under review are to be found in the Appendices to the Weber-Parkes Prize Essay, 1915. (In manuscript, Royal College of Physicians, London.

The Principle adopted for the Comparison of Cases Treated With or Without Tuberculin.

As already stated, tuberculin was not employed in the treatment of the graver and more acute cases. It is useless therefore to compare the results of two series of patients treated at the same time in the sanatorium, the one with, and the other without, the addition of tuberculin.

It is impossible to make allowance for the factor introduced by the selection of the more favourable cases for treatment with the inoculations.[1] The better method is to set out, and to compare the general results obtained in a total number of cases treated during one or more periods before tuberculin was used, side by side with the general results obtained in comparable cases during like periods since treatment with tuberculin was adopted. This gives a view of the effect of the use of tuberculin upon the results as a whole, and meets the difficulty raised by the selection of cases for the specific treatment. If tuberculin is of service, its value should be reflected in an improvement in the total results obtained since its adoption as compared with those formerly obtained. Should the records of the selected cases treated with the inoculations fail to improve the total results, there would be an indication that tuberculin, as an additional favourable factor in treatment, had had too slight an influence to be appreciable in statistics. This method meets another difficulty. When thus comparing cases, the question arises as to how treatment with tuberculin should be defined. It is contended by some that only those who receive the inoculations for some twelve months, or who reach a high level of tolerance, should be so considered; but by so doing the patients for whom tuberculin proved unsuitable or harmful are eliminated, thereby introducing the fallacy of selection. In this report, every case which received the inoculations is regarded as having been treated with tuberculin.

The Data available for Investigation.

The data consist of the records of 736 cases of pulmonary tuberculosis discharged from the sanatorium during the six years 1908, 1910, 1911, 1912, 1913, and 1914. In 1909 some patients were given small doses of tuberculin, although no systematic trial was made of this treatment; this year has therefore been omitted.

The six years covered by the observations are made up of consecutive periods each of three years' duration. During the first

[1] Perhaps, scientifically, the best method would be to classify all patients on admission as being suitable or not suitable for treatment with tuberculin, and thereafter of all those regarded as suitable to give tuberculin to patients whose names began with A to K, and general measures only to those whose names began with L to Z. The two groups of cases could be treated simultaneously, thus reducing the fallacy of selection to a minimum. It was considered, however, that this plan was too much in the nature of an experiment, and that if tuberculin were really of use it could not properly be withheld from some patients, presumably suitable for this treatment, merely for purposes of investigation.

period, sanatorium treatment alone was given to the patients, and during the second period tuberculin treatment was used extensively in addition to the general hygienic measures.

TABLE XIX

The Number of Cases Discharged during the first Three Years.

In 1908	115 cases
„ 1910	138 „
„ 1911	131 „
Total	384 cases

TABLE XX

The Number of Cases Discharged during the second Three Years, and the Number and Percentage of them which received Tuberculin.

Year	Number of Cases	Number of Cases which received Tuberculin	Percentage
1912	105	65	61·9
1913	116	94	81·0
1914	131	79	60·3
Total	352	238	67·6

The Condition before Treatment of the Cases Discharged during the Two Periods.

The value of statistics of results as a means of estimating the efficiency of various methods of treatment, depends to a large extent upon the degree in which the patients subjected to each method were comparable.

The equalization of the cases discharged during the two periods is therefore of importance. To this end they have been grouped in accordance with the system of classification described upon p. 7, but with one modification, namely that only those patients in whose sputum T. B. were demonstrated have been included in either series.

TABLE XXI

The Condition on Admission of the 384 Cases Discharged during the first Three Years.

Group	1908	1910	1911
1	29 cases	35 cases	37 cases
2	86 „	103 „	94 „
Total	115 cases	138 cases	131 cases

The Condition on Admission of the 352 Cases Discharged during the second Three Years.

Group	1912	1913	1914
1	21 cases	14 cases	26 cases
2	84 „	102 „	105 „
Total	105 cases	116 cases	131 cases

Cases of far advanced disease (Group 3) have not been considered, since it is generally recognized that tuberculin is not likely to benefit patients of this degree.

Cases diagnosed as pulmonary tuberculosis, but in which T. B. were not found in the sputum, have also been excluded so as to facilitate the equalization of the data. The inclusion of cases in the sputum of which T. B. were not found would necessitate a statement of the grounds of the positive diagnosis.

No method of classification, however, can be considered altogether satisfactory as a means of equalizing cases before treatment. The dividing line between the groups is an arbitrary one; it does not necessarily follow that every patient in Group 1 enjoys a better prognosis than those in Group 2. Therefore it is best to submit each series of patients to be compared to an analysis in respect of factors which have an important bearing upon the prospect of recovery.

The Detailed Comparison of the Cases

Table XXII

Sex. The Proportion of Males and Females included in each Year.

Year	Percentage of Males	Percentage of Females
1908	71·0	29·0
1910	67·3	32·7
1911	67·7	32·3
1912	66·7	33·3
1913	74·1	25·9
1914	64·4	35·6

Age. The following table shows the age distribution of the patients:—

Table XXIII

The Percentage of Cases in each age Grouping.

Year	Under 20 years	20–24 years	25–29 years	30–34 years	35–39 years	40–45 years	Over 45 years
1908	4·4	25·4	15·0	22·8	17·5	11·4	3·5
1910	6·6	22·5	27·0	25·3	8·4	6·3	3·5
1911	4·6	17·6	22·3	20·8	13·9	10·8	10·0
1912	3·8	27·7	22·9	11·4	15·2	9·5	9·5
1913	2·6	17·2	25·0	20·7	18·1	6·9	9·5
1914	6·8	16·6	17·5	15·7	18·4	19·7	5·3

The average age of all the cases discharged during the successive years is seen to vary but slightly.

Clinical Condition.

(a) *The Body Temperature.* In the following table, the cases are classified in accordance with their average daily temperature range during the first fifteen days after admission. The patients are divided into three groups according to the maximum of the daily excursion of the temperature.

TABLE XXIV

Year	Percentage of Patients who had a Daily Temperature Range		
	Not exceeding 99° F.	Exceeding 99° F. but not exceeding 99·9° F.	Rising to 100° F. or over
1908	39·4	52·6	8·0
1910	44·9	38·5	16·6
1911	46·9	46·1	7·0
1912	48·6	43·8	7·6
1913	53·4	40·5	6·1
1914	49·0	37·1	13·9

These records show that the proportion of cases which on admission had a daily temperature range not exceeding 99° F. has increased somewhat since 1908. The small number that had a febrile temperature is an indication of the favourable clinical character of the patients discharged during the six years, considered collectively.

(b) *The Body Weight.* The next table shows the percentage of cases in each year which, on admission, were up to or above their normal body weight, or were various amounts below it.

TABLE XXV

The Body Weight on Admission in Relation to the Normal Body Weight.

Year	Equal to or above	0 to 6 lb. below	7 to 13 lb. below	14 to 24 lb. below	Over 24 lb. below
1908	23·7	27·2	31·6	14·0	3·5
1910	49·2	18·2	23·9	8·7	nil
1911	50·0	16·2	18·5	12·3	3·0
1912	49·5	13·3	26·7	9·5	1·0
1913	44·0	19·0	20·7	14·6	1·7
1914	50·0	22·7	21·8	3·7	1·8

These records show a slight variation in favour of the cases discharged during the last three years.

(c) *The Extent of the Disease.* Table XXVI shows in each year the percentage of cases which had signs of disease in one, two, three, four, or five lobes, or had no abnormal physical signs in the lungs. A record is also given as to the percentage in which there was evidence of tuberculosis of the larynx.

TABLE XXVI

Year	nil definite	1 lobe	2 lobes	3 lobes	4 or 5 lobes	Tuberculosis of larynx
1908	3·5	22·0	50·9	18·4	5·2	20·0
1910	·7	17·6	46·5	29·6	5·6	17·0
1911	nil	26·9	36·2	33·1	3·8	27·0
1912	1·9	17·1	41·0	28·6	11·4	27·0
1913	nil	16·4	52·5	18·1	13·0	20·0
1914	1·5	21·2	47·7	22·9	6·7	16·7

The patients discharged during the first three years would appear from this table to have been somewhat more favourable than those discharged during the second three years. The explanation is that,

during the latter period, less definite evidence was accepted as indicative of disease; hence the higher percentage returned as with infection in four or five lobes.

(d) *The Probable Prognosis.* An attempt was made to classify the patients on admission in accordance with their probable prognosis. They were grouped in two classes, namely, those with a seemingly favourable and an unfavourable outlook respectively. This classification makes no pretence to a scientific grouping; it is but an index of clinical impressions.

TABLE XXVII

The Proportion of Favourable and Unfavourable Cases.

Year	Favourable	Unfavourable
1908	65·8	34·2
1910	75·3	24·7
1911	75·4	24·6
1912	69·5	30·5
1913	74·1	25·9
1914	75·9	24·1

Commentary.

The patients discharged during the successive years were comparable in all essentials. They formed approximately 58 per cent. of the total number discharged from the sanatorium during this period; the remaining 42 per cent. being made up of those in whom no T. B. were found, and those suffering from advanced pulmonary tuberculosis, in about equal proportions. Patients were selected before admission as being likely to respond favourably to treatment, and collectively their clinical condition was better than that of the average case of pulmonary tuberculosis throughout the general population.

Sahli,[1] apropos of statistical methods of estimating the value of tuberculin, lays down as a fundamental principle that 'every particular case in the whole series of statistics, whether treated with or without tuberculin, should be stringently chosen on the basis that it offers some prospect for successful treatment by this method'.

Sahli's condition has been complied with.

Length of Treatment.

The longer treatment is followed, providing it be efficient, the greater is the probability of a good result being obtained. This is equally true of immediate results as judged by arrest of the disease, restoration of health, and disappearance of T. B. from the sputum, and of subsequent results as estimated by the maintenance of life and capacity for work. The duration of treatment must then be considered. In this respect, the data for the years in which tuberculin was, and was not, used are not quite comparable; for after

[1] A Contribution to the Critical Study of Therapeutic Statistics, by Hermann Sahli, *British Medical Journal*, April 1914.

the adoption of the specific treatment, patients remained in the sanatorium longer than formerly.

Table XXVIII gives particulars as to the duration of treatment in the sanatorium. Treatment received after discharge from the institution has not been taken into account.

TABLE XXVIII

Percentage of Cases which were Treated in the Sanatorium for Various Periods.

Year	8–15 weeks	16–23 weeks	24–31 weeks	32–39 weeks	40–47 weeks	48–56 weeks	56 weeks and over
1908	39·5	33·3	18·4	7·0	·9	·9	nil
1910	26·7	45·7	20·4	3·7	2·7	nil	·8
1911	31·5	27·0	32·3	6·9	2·3	nil	nil
1912	29·5	31·4	16·1	8·5	9·5	3·0	2·0
1913	22·4	30·2	20·7	17·2	2·6	3·5	3·4
1914	31·8	31·8	21·8	11·3	nil	1·8	1·5

The following figures record in each year the percentage of cases which remained in the sanatorium for twenty-five weeks or more. The number of cases which the percentage figures represent is added.

TABLE XXIX

Patients Treated for 25 Weeks or more.

Year	Number of Patients	Percentage
1908	28	24·3
1910	29	21·0
1911	43	32·8
1912	40	38·1
1913	54	46·6
1914	39	29·8

The greater length of treatment enjoyed by the cases discharged during the second three years, especially in 1913, is a factor which must be taken into account when comparing the results obtained in the two periods.

A comparison is made later between the 'after-history' experience of the cases discharged during 1908, 1910, and 1911, and that of the cases discharged during 1912, 1913, and 1914. Of the first series of patients, 26 per cent. remained in the sanatorium for twenty-five weeks or more; whereas of the second series a higher proportion enjoyed this length of treatment, the figure for 1913 being 46·6 per cent. Those treated with tuberculin form the large majority of these cases, the production of a high level of tuberculin immunity requiring a longer period of residence than had hitherto prevailed. Again, thirty of the patients discharged during 1913 subsequently attended regularly at an 'After-Care' Tuberculin Dispensary.

The Immediate Results in Cases Treated With and Without Tuberculin.

The following statistics of 'immediate results' refer to the 384 cases which were treated in the sanatorium and discharged during the years 1908, 1910, 1911, and to the 352 cases, of which 238 or 67·6 per cent. received tuberculin, discharged during the years 1912, 1913, and 1914.

The General Results.

Table XXX records the general results obtained during these two periods (for definition of terms see page 8) :—

Table XXX

Condition on Discharge.

Year	Number of Cases	Percentage of Cases which received Tuberculin	Percentage Much Improved	Percentage Improved	Percentage Stationary or Worse
1908	115	nil	70·2	17·5	12·3
1910	138	nil	68·1	22·5	9·4
1911	131	nil	73·1	10·0	16·9
Total	384	—	—	—	—
1912	105	61·9	59·0	21·9	19·1
1913	116	81·0	64·6	12·9	22·5
1914	131	60·3	73·7	7·5	18·8
Total	352	—	—	—	—

In the above table cases in which the disease appeared to be 'ARRESTED' are included in the group 'MUCH IMPROVED'.

The general results obtained in the two periods are practically the same. Little or no significance can be attached to slight differences in the percentage figures. The addition of tuberculin to the usual methods of treatment did not influence the statistics favourably; the best results obtained since its adoption occurred in 1914, the year in which the slow method of administration was employed.

The results in the cases treated with tuberculin may be set out separately :—

Table XXXI

The Results in 228 Selected Cases Treated with Tuberculin.

Condition on Discharge	Number of Cases	Per Cent.
Much Improved	176	77·2
Improved	22	9·6
Stationary or Worse	30	13·2
Total	228	100·0

The following are the results obtained in 240 similarly selected cases treated in the sanatorium prior to the adoption of tuberculin.

TABLE XXXII

Condition on Discharge	Number of Cases	Per Cent.
Much Improved	180	75·0
Improved	29	12·1
Stationary or Worse	31	12·9
Total	240	100·0

These results are almost identical with those of the selected cases treated with tuberculin.

The Immediate Results as estimated by the Disappearance of T. B. from the Sputum

The comparison of the results, as judged by the disappearance of T. B. from the sputum, calls for especial notice, since it has been stated that the combination of tuberculin inoculations with sanatorium treatment is more effective in causing disappearance of the bacilli than the general measures alone.

The significance of the disappearance of the characteristic organisms from the sputum during treatment in the sanatorium lies in the fact that cases in which this occurs show better 'after-histories' than those in which this result is not attained. (*Vide* Chapter V of this report.)

Statistics of Sputum Records.

Table XXXIII gives the sputum records in the cases discharged during the successive years.

TABLE XXXIII

Year	Number of Cases	Percentage which received Tuberculin	Number in which T. B. disappeared from the Sputum	Percentage
1908	115	nil	29	25·2
1910	138	nil	43	31·1
1911	131	nil	29	22·1
1912	105	61·9	30	28·6
1913	116	81·0	25	21·6
1914	131	60·3	39	29·8

These results show but slight variation. Their close agreement is well shown by the summary in Table XXXIV.

TABLE XXXIV

Records for Year	Number of Cases discharged	T. B. disappeared from the Sputum	
		Number of Cases	Percentage
1908, 1910, 1911	384, of which none received Tuberculin	101	26·3
1912, 1913, 1914	352, of which 238 or 67·6 per cent. received Tuberculin	94	26·7

A further analysis of the sputum records shows that when cases are selected to the exclusion of all save those with a single lesion of limited extent, associated with an absence of constitutional

symptoms, the percentage figures for disappearance of T. B. are as high as 50 per cent. both in patients treated with and without tuberculin.

The Subsequent Results as deduced from the Mortality Rates experienced by Cases Treated With and Without Tuberculin.

The data are made up of the 'after-history' records of the same patients whose 'immediate', results of treatment have just been considered.

They therefore refer to the 384 patients who were treated in the sanatorium without tuberculin, and discharged during the years 1908, 1910, and 1911, and to the 352 patients who were treated in the same institution and discharged during the years 1912, 1913, and 1914, a period in which tuberculin was largely used as an additional means of treatment.

To bring this section exactly into line with other sections of the report, the data have been revised slightly so as to exclude all cases which were under treatment in the sanatorium for less than eight weeks. The number of cases eliminated from the first period (tuberculin control) is 11, and from the latter (tuberculin period) 9; the totals therefore being 373 and 343 respectively. Of the latter 343 patients, 235 received tuberculin. The exclusion of twenty cases, amounting to only 2·7 of the total considered, is unimportant. On investigation it was found to favour slightly the tuberculin years. It may be emphasized that every case which was discharged in the six specified years is included, provided it complied with the three following conditions:

(1) Admitted in Group 1 or Group 2.

(2) T. B. present in the sputum.

(3) Received at least eight weeks' treatment at the sanatorium.

In the first instance each case was observed up to the anniversary of discharge in 1916, the date 'last heard of' or the date of death as the case may be.

The general results are given in Tables 17–28 (*see* Appendix A). The comparisons of 'actual deaths' to 'expected deaths' are, however, given in the following Table XXXV.

Table XXXV

Classification	Ratio of Actual Deaths to Expected Deaths	
	Males	Females
Group 1		
Tuberculin Control Years	9·5	11·3
Tuberculin Years	7·2	11·8
Group 2		
Tuberculin Control Years	15·7	24·5
Tuberculin Years	17·1	28·4
Groups 1 and 2		
Tuberculin Control Years	13·6	21·5
Tuberculin Years	15·5	25·6

Taking Groups 1 and 2 together the results for the tuberculin control period are, for both males and females, slightly better than those for the tuberculin years. This applies also to Group 2 males and females, and to Group 1 females. Group 1 males is the only result in which the position is reversed.

It should, however, be borne in mind that the tuberculin control years included patients discharged in 1908, 1910, and 1911; whereas the tuberculin years refer to cases discharged in 1912, 1913, and 1914. The former have therefore been observed for several years longer than the latter. This favours the tuberculin control, since, as has already been shown, the excessive mortality experienced by consumptives declines considerably after the first few years since discharge.

In order to equalize the data in this respect the 'tuberculin control' has been truncated so that no experience is included after the first four years since discharge, four years being the maximum period during which a case discharged in the 'tuberculin years' could have been observed.

The procedure modifies the results slightly, as is seen in the following Table XXXVI.

TABLE XXXVI

Tuberculin Control Years.

Mortality Experience limited to the first Four Years after Discharge.

Group	Males			Females		
	Actual Deaths	Expected Deaths	Ratio of Actual to Expected	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
Group 1	22	1·976	11·1	6	·445	13·5
Group 2	73	3·805	19·2	39	1·568	24·9
Groups 1 and 2	95	5·781	16·4	45	2·013	22·4

Thus, both in Groups 1 and 2, the results for the males are slightly more favourable for the 'tuberculin years' than for the 'control years'. In respect of the females in Group 1, the same result obtains, but for those in Group 2, and in Groups 1 and 2 combined, the mortality rates for the 'control years' are somewhat lower. In no instance is there any marked difference between the results.

Taking the whole of the patients together, combining both groups and both sexes, the ratio of 'actual deaths' to 'expected deaths' is 18·0 for the 'control period' and 18·1 for the 'tuberculin period'. Although as between the sexes and Groups on admission the results show slight variations, which are probably due to the small body of data available for observation, when the groupings and sexes are combined throughout the results are exactly the same.

An endeavour was made to carry the investigation further and to analyse the experience of the patients who actually received the tuberculin injections. These patients, who constitute about 68 per

cent. of those discharged during the 'tuberculin period', would be expected to show better results than the remaining 32 per cent., since, with few exceptions, the latter were of a less favourable type, and not considered suitable for the special treatment.

It is necessary to have some standard by which to measure the cases treated with tuberculin. The fallacies inherent in attempts to compare one group of patients with another have been discussed previously. In this instance it was decided to select from the patients treated during the control period a similar number of cases as received tuberculin treatment, this number to be comparable with the tuberculin treated cases in regard to sex, age, general clinical condition, degree of fever, prognosis at admission, &c. Every effort was made to select a group of cases which should as nearly as possible present the same prospects for recovery as those who received tuberculin. With a view of eliminating any unconscious personal bias the selection was made by a third party; it is admitted that several slightly different selections might have been made upon the same basis.

The number of patients who received tuberculin was 238, of which 168 were males and 70 females; therefore, from the 'control years' a similar number were selected of each sex. Every case included in the control and the tuberculin treated groups had T. B. in the sputum, but in neither instance were any patients excluded on account of the period of stay at the Institution being less than eight weeks. Further, as a result of a special inquiry addressed to the patients it was found possible to observe them up to the anniversary of discharge in 1917. The 'control years' were truncated for the same reasons as before, but after the completion of five instead of four years following discharge.

The results are tabulated in Table XXXVII.

Table XXXVII

Comparison between the mortality of

(a) *Cases selected from the Tuberculin Control Years (first five years' experience only);*

(b) *Cases which were actually treated with Tuberculin, and observed up to anniversary of discharge in 1917.*

No Cases excluded

Classification	Ratio of Actual Deaths to Expected	
	Males	Females
Group 1		
Control Years	7·4	19·2
Tuberculin	12·1	8·5
Group 2		
Control Years	16·3	21·7
Tuberculin	16·2	21·1
Groups 1 and 2		
Control Years	14·2	21·3
Tuberculin	15·4	18·6

As far as Group 1 is concerned the results are contradictory, the rates of mortality of the males who received tuberculin and the females in the 'control years' being much higher than would be expected. This may be due to the small number of observations. In Group 2, where the number of years of life observed is nearly four times as great as in Group 1, the results for the tuberculin treated cases and the control cases are practically the same. Taking the groups together the 'control years' show slightly better results for the males, but slightly worse for the females. Combining both sexes and both groups together the ratios are practically identical, namely 15·9 for the control and 16·1 for the tuberculin treated. Making allowance for the element of fallacy associated with a comparison of two groups of selected cases, it is at least highly suggestive that the result just given so closely confirms that shown in the previous comparison of unselected cases. When considering the various results, the more prolonged residence in the sanatorium which prevailed during the tuberculin period must be borne in mind.

Conclusions.

Collectively, the results point to the conclusion that tuberculin treatment, when given in addition to the usual measures practised in the sanatorium, had no appreciable effect either for good or ill. Possibly the Group 1 cases may have benefited slightly when given tuberculin: however, the data for this group are small; the more extended stay in the sanatorium of these cases also has to be allowed for.

Unquestionably many patients who received tuberculin treatment made good recoveries, but there are no grounds for supposing that they would not have progressed as satisfactorily had the injections been withheld: certainly, comparable cases treated without tuberculin gave no less favourable results. The fact that the records of the tuberculin years show no improvement over those for the control years gains in significance when it is remembered that, as shown in this Report, treatment in a sanatorium is far from an efficient means of curing tuberculosis. With so much scope for improvement in sanatorium results, the value of any remedy of real potency for good could be established without difficulty within a relatively short period. The conclusions arrived at as to the value of tuberculin, which was introduced as something in the nature of a specific remedy for tuberculosis, must be deemed distinctly disappointing.

CHAPTER IV

Mortality Rates determined according to Type of Onset of the Disease.

From a study of the histories of their illness given by a number of individuals suffering from pulmonary tuberculosis, it is learnt that there is considerable variation in the way in which the disease first manifests itself. In some cases the first symptom noticed is spitting of blood, termed haemoptysis: less commonly the commencement of the disease is associated with an attack of pleurisy, with or without an effusion into the pleural cavity. Again, a type of onset which is frequently given is that of a gradual loss of strength accompanied by cough. In cases of the last type the symptoms often have developed so insidiously that the patient cannot state when they first made their appearance. It seemed that an investigation of the mortality rates experienced by the various groups of patients, classified in accordance with the type of onset of their disease, might give results of interest and practical value. For instance, should it be demonstrated that certain symptoms are associated with mortality rates which are better or worse than those of the patients as a whole, the fact would have a distinct bearing upon prognosis.

The patients therefore have been divided into three groups, according to whether the type of onset was associated with haemoptysis, or pleurisy, or was of an insidious character.

By haemoptysis is meant what the medical profession term a frank haemoptysis, namely the coughing up of an appreciable amount of blood. Cases in which 'coloured' or 'streaked' sputum only occurred are not included.

By pleurisy is meant definite inflammation of the pleura, to be recognized by the existence of friction sounds, or a pleurisy with effusion. Pain in the chest without such objective evidence of the condition has not been considered sufficient evidence of pleurisy. The term insidious needs no definition.

The distribution of the cases in the various groups indicating condition on admission and type of onset are given in Tables XXXVIII and XXXIX. The headings a, b, and c have the same significance as on the classification card, viz. haemoptysis, pleurisy, and cough respectively.

Table XXXVIII

Number of Male Patients 1,053.

Age Group	Group 1 Type of Onset				Group 2 Type of Onset				Group 3 Type of Onset				All Groups Type of Onset			
	a	b	c	all	a	b	c	all	a	b	c	all	a	b	c	all
-22	16	4	28	48	12	9	40	61	7	2	9	18	35	15	77	127
23-27	24	7	41	72	26	8	90	124	8	6	39	53	58	21	170	249
28-32	24	8	37	69	27	15	64	106	8	4	32	44	59	27	133	219
33-37	12	8	27	47	31	13	55	99	5	8	26	39	48	29	108	185
38-42	6	3	11	20	21	10	45	76	3	1	20	24	30	14	76	120
43-	7	4	22	33	19	6	50	75	10	3	32	45	36	13	104	153
Total	89	34	166	289	136	61	344	541	41	24	158	223	266	119	668	1053
Age Group	Percentages				Percentages				Percentages				Percentages			
	a	b	c	all	a	b	c	all	a	b	c	all	a	b	c	all
-22	5·5	1·4	9·7	16·6	2·2	1·7	7·4	11·3	3·1	·9	4·1	8·1	3·3	1·4	7·3	12·0
23-27	8·3	2·4	14·2	24·9	4·8	1·5	16·6	22·9	3·6	2·7	17·5	23·8	5·5	2·0	16·1	23·6
28-32	8·3	2·8	12·8	23·9	5·0	2·8	11·8	19·6	3·6	1·8	14·3	19·7	5·6	2·6	12·6	20·8
33-37	4·2	2·8	9·3	16·3	5·7	2·4	10·2	18·3	2·2	3·6	11·7	17·5	4·6	2·8	10·3	17·7
38-42	2·1	1·0	3·8	6·9	3·9	1·8	8·3	14·0	1·3	·5	9·0	10·8	2·9	1·3	7·2	11·4
43-	2·4	1·4	7·6	11·4	3·5	1·1	9·3	13·9	4·5	1·3	14·3	20·1	3·4	1·2	9·9	14·5
Total	30·8	11·8	57·4	100·0	25·1	11·3	63·6	100·0	18·3	10·8	70·9	100·0	25·3	11·3	63·4	100·0

Table XXXIX

Number of Female Patients 654.

Age Group	Group 1 Type of Onset				Group 2 Type of Onset				Group 3 Type of Onset				All Groups Type of Onset			
	a	b	c	all	a	b	c	all	a	b	c	all	a	b	c	all
-22	5	3	12	20	3	3	27	33	4	2	18	24	12	8	57	77
23-27	7	7	32	46	12	14	55	81	3	7	29	39	22	28	116	166
28-32	7	4	39	50	10	6	45	61	6	6	34	46	23	16	118	157
33-37	6	4	18	28	11	7	37	55	6	3	15	24	23	14	70	107
38-42	3		10	13	8	3	29	40	3		14	17	14	3	53	70
43-	3		11	14	4	4	29	37	3	2	21	26	10	6	61	77
Total	31	18	122	171	48	37	222	307	25	20	131	176	104	75	475	654
Age Group	Percentages				Percentages				Percentages				Percentages			
	a	b	c	all	a	b		all	a	b	c	all	a	b	c	all
-22	2·9	1·8	7·0	11·7	1·0	1·0	8·7	10·7	2·3	1·1	10·2	13·6	1·9	1·2	8·7	11·8
23-27	4·1	4·1	18·7	26·9	4·0	4·5	17·9	26·4	1·7	4·0	16·5	22·2	3·4	4·3	17·7	25·4
28-32	4·1	2·3	22·8	29·2	3·2	2·0	14·6	19·8	3·4	3·4	19·3	26·1	3·5	2·5	18·0	24·0
33-37	3·5	2·3	10·5	16·3	3·5	2·3	12·1	17·9	3·4	1·7	8·5	13·6	3·5	2·1	10·7	16·3
38-42	1·8		5·9	7·7	2·6	1·0	9·5	13·1	1·7		8·0	9·7	2·1	·5	8·1	10·7
43-	1·8		6·4	8·2	1·3	1·3	9·5	12·1	1·7	1·1	12·0	14·8	1·5	·9	9·4	11·8
Total	18·2	10·5	71·3	100·0	15·6	12·1	72·3	100·0	14·2	11·3	74·5	100·0	15·9	11·5	72·6	100·0

The first point to be noted in the examination of these tables is the proportion of the cases of each type of onset considered apart from the condition on admission. The type contributing the smallest number of cases is that of pleurisy, the percentage being little over 11 for each sex. Type (a) haemoptysis shows a percentage of 25·3 and 15·9 respectively for males and females; while type (c) cough, &c. is the largest group, showing a percentage of 63·4 for males and 72·6 for females. These proportions are almost exactly reproduced in Group 2 taken by itself. Group 3 shows a slightly different distribution, including as it does for both sexes a larger proportion of cases of type (c). but a smaller proportion of type (a). Group 1 shows a variation in type of onset to about the same degree as Group 3, but in an opposite direction; that is, it comprises a larger percentage of type (a) cases and an almost correspondingly smaller proportion of type (c).

The distribution of the cases in respect of the age at discharge does not present any characteristics that call for special notice.

The main features of the distribution are :—

(1) That in the case of about two-thirds of the patients the disease commenced insidiously, and in about one-fifth with haemoptysis.

(2) That, as compared with the females, the males include a larger percentage of patients whose disease commenced with haemoptysis; this is combined with a correspondingly smaller number in whom the disease began insidiously.

(3) That this distribution as between the sexes persists in each of the three groups on admission; but is most marked in Group 1, and least in evidence in Group 3.

The mortality experienced can be seen from the ratios of 'actual' to 'expected deaths' in the following Table XL; full particulars as to the number of patients, years of life, actual and expected deaths for each age group are given in the Tables 29–34 (*see* Appendix A).

TABLE XL

Ratios of Actual Deaths to Expected Deaths according to Type of Onset.

Type of Onset	Group 1		Group 2		Group 3		All Groups	
	Male	Female	Male	Female	Male	Female	Male	Female
Haemoptysis (a)	5·1	4·5	11·6	12·5	30·0	47·0	11·4	14·7
Pleurisy (b)	11·3	10·0	11·0	24·8	40·3	21·0	14·7	20·1
Cough, &c. (c)	6·1	4·1	18·5	19·6	42·5	39·7	17·9	18·7

It will be noticed that for 'All Groups', both among males and females, type (a) shows more favourable rates than types (b) and (c). With a view to its possibly throwing some light upon these facts Table XLI has been constructed, showing the distribution of the cases for each type of onset in respect of each group on admission.

TABLE XLI

		Males		Females	
		Number	Percentage	Number	Percentage
Haemoptysis (a)	Group 1	89	33·5	31	29·8
	,, 2	136	51·1	48	46·2
	,, 3	41	15·4	25	24·0
All Groups		266	100·0	104	100·0
Pleurisy (b)	Group 1	34	28·6	18	24·0
	,, 2	61	51·3	37	49·3
	,, 3	24	20·1	20	26·7
All Groups		119	100·0	75	100·0
Cough, &c. (c)	Group 1	166	24·9	122	25·7
	,, 2	344	51·5	222	46·7
	,, 3	158	23·6	131	27·6
All Groups		668	100·0	475	100·0

An examination of this table discloses that on their admission to the sanatorium a larger percentage of patients were classified as of Group 1 when the type of onset was given as haemoptysis than when the onset was of an insidious character, the percentages being 33·5 and 24·9 respectively for the males and 29·8 and 25·7 for the females. The table shows also that patients with an onset of type (c) included a proportionately greater number of cases admitted in a condition consistent with Group 3 than was the case with patients giving an onset of type (a). These features are particularly marked in the male distribution; they are also present, although to a lesser degree, in that of the female. It is probably owing to the fact that in respect of the males, the records for an onset of type (a) include 33·5 per cent. of cases of Group 1 and 15·4 per cent. of Group 3 as compared with 29·8 and 24·0 per cent. respectively shown by the records of the females, that the males of type (a) appear to experience lighter mortality than the females of the same type. It would therefore seem that the percentage of cases of each group on admission found to be present in each of the three types of onset would of itself be sufficient to explain the reason the cases of haemoptysis show the lighter mortality exhibited for 'All Groups' in Table XL. If, however, reference be made to the other ratios in Table XL it will be seen that the superiority of cases of type (a) over those of type (c) persists generally in each group on admission; the superiority is only slight in Group 1, but exceedingly well marked in Group 2, which includes by far the largest number of patients. In this connexion it may be noted that Tables XXXVIII and XXXIX show that cases of Group 2 with an insidious onset occur relatively more frequently at the younger ages, i.e. below 33, than those cases in which the disease commenced with haemoptysis. A comparison of Tables 29 and 30 with Tables 33 and 34 (*see* Appendix A) shows, however, that in this group the relative superiority in mortality rates experienced by patients with an onset of haemoptysis is still in evidence even when consideration is extended to the results obtained in respect of cases included in the different age groupings.

It will be noted further that the proportion of Group 2 cases included in each type is practically constant, viz. 51 per cent. for males and 47 per cent. for females. Cases of Group 1 with a pleuritic onset show substantially higher rates of mortality than the other types; the number of patients under observation in this classification is, however, rather small, and it is not possible to say whether the inferiority is due to the paucity of data or to probable experience.

A Comparison with the Adirondack results relative to Haemoptysis.

When dealing with the Adirondack records Elderton and Perry determined the mortality experienced by all cases which at some time had suffered from haemoptysis. This is another matter from the consideration of the mortality of cases in which the onset of the disease was of the haemoptysis type, since many cases which commence insidiously or with pleurisy suffer from haemoptysis during the course of their illness. Haemoptysis is perhaps the commonest symptom of chronic consumption, and one which is frequently followed by an extension of the disease. Thus, the Midhurst and Adirondack experiences are not strictly comparable in this respect. Despite this fact, a comparison between the two experiences presents points of interest. As in the comparison previously made, the records of the Adirondack Sanatorium have been truncated so as to include no experience subsequent to the ninth year since admission. The 'expected deaths' for Adirondack were calculated on the basis of the English Life Table No. 6, and although the Midhurst experience is being analysed on the basis of the English Life Table No. 8, a fairly accurate comparison can be made by increasing the 'expected deaths' at Midhurst by one-third or by reducing the ratios by a quarter. It is understood that only cases of definite haemoptysis are included in both experiences.

TABLE XLII

Experience of Cases in which Haemoptysis is known to have occurred (Adirondack).

	Males			Females		
	Actual Deaths	Expected Deaths	Ratio of Actual to Expected	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
Incipient	32	6·2	5·2	11	4·5	2·4
Advanced	135	11·5	11·7	89	8·1	11·0
Far Advanced	24	·6	40·0	12	·4	30·0

Commenting upon the above figures, Elderton and Perry state 'that as a whole the mortality among the incipient cases which had had haemoptysis was considerably heavier than among the cases who had not had it, but in the advanced cases the excess was less. Haemoptysis seems to increase the mortality in the case of male lives and decrease it in the case of females; the difference in the latter case is, however, slight.' This is probably the case, since

among the Adirondack cases haemoptysis was not limited to an initial haemoptysis.

In Table XLIII the ratios of actual to expected deaths at Midhurst have been adjusted to allow for the difference in the mortality standard.

TABLE XLIII

Type of Onset—Haemoptysis.

Ratio of Actual Deaths to Expected calculated by the English Life Table No. 6 (Midhurst).

	Males	Females
Group 1	3·7	3·2
Group 2	8·5	8·8
Group 3	21·9	32·9

Bearing in mind that, as already stated, the two experiences are not really comparable, the results just given show a considerable measure of agreement. For example, it will be observed that for Group 1, both sexes combined, the figures for Midhurst and Adirondack are almost identical, while for Groups 2 and 3 the Midhurst results are the better; from the nature of the classification this would be expected.

These results point to the following conclusions:—

(1) That patients whose disease commenced with haemoptysis were on the whole diagnosed in a somewhat earlier stage than those in whom the disease began with pleurisy or more insidiously with cough, loss of weight and strength: in this respect the latter type are the least favourable.

(2) That patients whose chief initial symptom was haemoptysis have experienced lighter rates of mortality than those in whom the disease manifested itself in a more insidious manner.

(3) That this characteristic is a feature of each of the three groups on admission, suggesting that an initial haemoptysis may be associated with a relatively less severe type of disease.

The high proportion of cases giving a history of an insidious onset, which on admission had to be classed in Group 3, is evidence that there exists considerable danger of the disease being overlooked, when its earliest manifestations, unlike haemoptysis or acute pleurisy, are not such as imperatively to demand immediate treatment.

CHAPTER V

RATES OF MORTALITY DETERMINED IN RESPECT OF THE PRESENCE OR ABSENCE OF TUBERCLE BACILLI IN THE SPUTUM.

THE demonstration of tubercle bacilli in the sputum of an individual is of considerable significance, since it definitely establishes the diagnosis of pulmonary tuberculosis. In the absence

of this conclusive bacteriological proof, the disease is to be recognized by an association of signs and symptoms only. Under these circumstances there is room for error in diagnosis, for although in many instances the existence of tuberculosis may be asserted with confidence, in others it is impossible to say more than that the conditions present are strongly suggestive of the disease. Again, granting the correctness of a positive diagnosis, the fact that tubercle bacilli are not present in the sputum shows the condition to be what is termed 'closed tuberculosis', which represents a less advanced stage of the disease than that designated 'open tuberculosis'. This latter term is employed when tubercle bacilli are present in the sputum, in which case it is to be recognized that the lung structures have begun to break down. For these reasons a greater proportion of recoveries and better rates of mortality are to be expected among patients in whose sputum tubercle bacilli cannot be demonstrated, than among those whose sputum contains the characteristic bacillus. Clinical experience shows that such is the case.

Similarly, the disappearance of tubercle bacilli from the sputum in which these organisms previously had been found is to be recognized as of favourable import, as indicative that the case of 'open tuberculosis' has become one of 'closed tuberculosis'; in other words, that the disease in the lungs is in process of or has undergone 'arrest'. Thus, bacteriologically proven cases, from the sputum of which tubercle bacilli disappear, would be expected to show better results than cases in which the bacilli are constantly to be demonstrated in the sputum.

This particular investigation was undertaken with a view to ascertaining whether indeed the presence or absence of tubercle bacilli in the sputum, or the disappearance of the bacilli, are sufficiently potent factors to be reflected in mortality rates.

Examination of Sputum.

In the case of each patient on admission to the sanatorium the sputum was carefully examined; subsequently examinations were made every four weeks. A sputum recorded as negative therefore represents the result of a searching examination.

On the basis of the results of the sputum examination the patients have been divided into three groups, as follows:—

(1) Where tubercle bacilli were not found either at admission or at discharge, or at any intermediate date:—styled − −;

(2) Where tubercle bacilli were present at admission but were not in evidence at discharge:—styled + −;

(3) Where tubercle bacilli were present both at admission and discharge:—styled + +.

Particulars of the number of cases occurring in each of these three groupings considered in relation to the condition on admission are given in Tables XLIV and XLV.

Table XLIV

Number of Male Patients 1,053.

Age Group	Group 1 Number 289 Sputum			Group 2 Number 541 Sputum			Group 3 Number 223 Sputum			All Groups Number 1,053 Sputum		
	− −	+ −	+ +	− −	+ −	+ +	− −	+ −	+ +	− −	+ −	+ +
-22	16	15	17	5	12	44		2	16	21	29	77
23-27	15	34	23	7	34	83	1	4	48	23	72	154
28-32	11	30	28	4	24	78	1	2	41	16	56	147
33-37	12	17	18	5	26	68	1	2	36	18	45	122
38-42	3	7	10	3	14	59		1	23	6	22	92
43-	8	8	17	2	18	55	2	6	37	12	32	109
Total	65	111	113	26	128	387	5	17	201	96	256	701

Age Group	Percentage			Percentage			Percentage			Percentage		
	− −	+ −	+ +	− −	+ −	+ +	− −	+ −	+ +	− −	+ −	+ +
-22	5·5	5·2	5·9	·9	2·2	8·1		·9	7·1	2·	2·8	7·3
23-27	5·2	11·8	8·0	1·3	6·3	15·3	·5	1·8	21·5	2·2	6·8	14·6
28-32	3·8	10·3	9·7	·7	4·5	14·4	·5	·9	18·4	1·5	5·3	14·0
33-37	4·2	5·9	6·2	·9	4·8	12·6	·5	·9	16·1	1·7	4·3	11·6
38-42	1·0	2·4	3·4	·6	2·6	10·9		·5	10·3	·6	2·1	8·7
43-	2·8	2·8	5·9	·4	3·3	10·2	·9	2·6	16·6	1·1	3·0	10·4
Total	22·5	38·4	39·1	4·8	23·7	71·5	2·4	7·6	90·0	9·1	24·3	66·6

Table XLV

Number of Female Patients 654.

Age Group	Group 1 Number 171 Sputum			Group 2 Number 307 Sputum			Group 3 Number 176 Sputum			All Groups Number 654 Sputum		
	− −	+ −	+ +	− −	+ −	+ +	− −	+ −	+ +	− −	+ −	+ +
-22	10	7	3	2	11	20		4	20	12	22	43
23-27	17	19	10	6	20	55		3	36	23	42	101
28-32	23	19	8	3	14	44		6	40	26	39	92
33-37	15	9	4	9	13	33		3	21	24	25	58
38-42	7	3	3	6	7	27		1	16	13	11	46
43-	6	6	2	7	9	21	1	3	22	14	18	45
Total	78	63	30	33	74	200	1	20	155	112	157	385

Age Group	Percentage			Percentage			Percentage			Percentage		
	− −	+ −	+ +	− −	+ −	+ +	− −	+ −	+ +	− −	+ −	+ +
-22	5·8	4·1	1·8	·7	3·6	6·5		2·3	11·4	1·8	3·3	6·6
23-27	9·9	11·1	5·8	2·0	6·5	17·9		1·7	20·4	3·5	6·4	15·4
28-32	13·5	11·1	4·7	·9	4·6	14·3		3·4	22·7	4·0	6·0	14·1
33-37	8·8	5·2	2·3	2·9	4·2	10·8		1·7	11·9	3·7	3·8	8·9
38-42	4·1	1·8	1·8	2·0	2·3	8·8		·6	9·1	2·0	1·7	7·0
43-	3·5	3·5	1·2	2·3	2·9	6·8	·6	1·7	12·5	2·1	2·8	6·9
Total	45·6	36·8	17·6	10·8	24·1	65·1	·6	11·4	88·0	17·1	24·0	58·9

It will be noticed that the + + cases include more than one-half of the total discharges of both sexes. There is relatively a larger number of + + cases and a smaller number of − − cases in the male section than in the female section; the proportion of + − cases is the same for each sex. The number of − − cases in the female section is not only proportionately larger than those in the male section, but is actually so numerically. A little over 36 per cent. of the patients were discharged with a negative sputum: this fact adds some further significance to the mortality rates shown in Chapter I.

Taking the groups on admission separately it will be noticed that in Group 1 both sexes show approximately the same proportion of + − cases, but the males as compared with the females include over twice the percentage of + + cases and only one-half of − − cases. The inference is that in the case of the females the disease was diagnosed at an earlier stage than was the case among the males; this may well be due to the reluctance of the male patients, who are usually the principal or sole wage-earners, to recognize that they are suffering from ill health, and even to seek treatment when the truth is borne in upon them. Women, on the other hand, are usually able to lay aside their duties and go away to a sanatorium with less fear of dislocating the finances of the household.

The features of Group 2 as between the sexes are similar to those of Group 1, but different in extent. As would be expected, the number of + + cases is largely increased, the percentage of + − cases is much less, and the − − cases constitute only a little less than 7 per cent. of the total number discharged of that group.

In Group 3 about 90 per cent. of the cases are + + and 9 per cent. are + − ; the number of cases classified as − − in this group is only 6, of which 5 are males.

Table XLVI gives the mortality in summary form; the full tables will be found in Appendix A, Tables 35–40.

Table XLVI

Ratio of Actual Deaths to Expected Deaths, in accordance with the Results obtained from Examinations of Sputum.

Class	Group 1		Group 2		Group 3		All Groups	
	Male	Female	Male	Female	Male	Female	Male	Female
− −	3·7	2·5	9·6	4·2	11·6	0 (1)[1]	5·5	3·1
+ −	5·2	4·5	5·9	7·7	18·4	21·3	6·5	7·7
+ +	8·8	11·8	19·9	29·6	44·2	39·9	21·8	31·6

It will be noticed that the T. B. − − cases show the lowest mortality rates, and the + + cases the highest:—the + − cases, as might be expected, occupy the intermediate position. There is only one exception to this, namely among the males in Group 2, where the − − cases show mortality rates considerably in excess of

[1] One case discharged, but 'lost sight of' at duration 0.

the + — cases. There are, however, only 59 — — cases in the whole of Group 2 : the paucity of the data is therefore the probable cause of the variation.

A pronounced and interesting feature in this table is the comparatively slight difference revealed between the mortality rates for the — — and the + — cases. The mortality rates of the + + cases are, however, by contrast much heavier than the + — cases.

As a matter of interest an endeavour was made to ascertain the mortality rates experienced by the class of patients presenting the most favourable prospects for recovery. It was thought that this class would be represented best by a combination of the following classifications :—

Condition on admission	Group 1
Condition on discharge	Arrested
Sputum	— —

Every case which complied with these three conditions is included in the following analysis :—

TABLE XLVII

Particulars relative to Patients Admitted in Group 1, Discharged Arrested, with a Negative Sputum both at Admission and Discharge.

Sex	Number of Patients	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
Males	57	327	6	2·287	2.6
Females	66	394	6	2·148	2·8
Total	123	721	12	4·435	2·7

There are 123 patients who can be classed in this particular category ; the number of females again predominating over the males. Since discharge they have been observed for 721 years. Of these patients only 6 males and 6 females, or 12 in all, have died. Their mortality, however, is more than two and one-half times that experienced by the general population. The ratio of 'actual deaths' to those 'expected' is seen to be practically the same for both sexes: having regard to the comparatively small number of cases under observation this is a remarkable confirmation in results.

Conclusions.

The results of this investigation thus support the general opinion as to the importance attaching to the presence or absence of tubercle bacilli in the sputum. The mortality figures indicate that cases in which tubercle bacilli have not been demonstrated in the sputum enjoy a substantially better prospect than those in which diagnosis has been confirmed by this 'positive' bacteriological find.

A fact of considerable practical bearing, and one which is by no means generally realized, is that patients admitted to a sanatorium

with a positive sputum who are discharged (+ −) with their sputum free of the tubercle bacillus enjoy but a slightly less favourable prognosis than patients in whom the characteristic organisms have never been demonstrated (− −).

With respect to the + + cases, namely those in which the tubercle bacilli were constantly to be found, while it is true that many instances occur of individuals living long and useful lives, throughout which tubercle bacilli are present in the sputum, the fact is established that as a class they have a distinctly unfavourable outlook, as compared with the + − and the − − cases.

The disappearance of the tubercle bacilli from the sputum must therefore be looked upon as a most important criterion of successful treatment. To secure a favourable prospect of making a permanent recovery, treatment should be continued until a negative sputum has been obtained.

Lastly, the results obtained among the − − cases and among those of the group selected as presenting an association of the most favourable factors, which show that their mortality is appreciably in excess of the normal, is an indication that pulmonary tuberculosis, even in its earliest stages, and when submitted to the best available treatment, greatly prejudices prospects of longevity. The mortality among this group of − − cases, when due to pulmonary tuberculosis, may be regarded as strong evidence in favour of correctness of the original diagnosis. This confirms clinical experiences, that although the finding of the tubercle bacillus establishes a diagnosis beyond any question, the disease is to be recognized with some measure of certainty in the absence of the specific organism.

CHAPTER VI

Mortality Rates among Cases in which there existed Tuberculosis of the Larynx.

Primary tuberculosis of the larynx is rarely met with, the condition almost invariably existing in association with tuberculous disease of the lung. Commonly, infection of the larynx is found in patients suffering from pulmonary tuberculosis in the more advanced stages; however, the systematic examination of the larynx of every patient shows that incipient disease of this region is not infrequently present when altogether unsuspected, and when the disease in the lungs is but slightly advanced. The involvement of the larynx under any circumstances is a serious complication in a case of pulmonary disease, so much so that, save for a few exceptionally favourable cases, a patient who presents evidence of tuberculosis of the larynx is at once excluded from Group 1, even though qualified for inclusion in this group upon other grounds.

Similarly, in the same circumstances, many cases otherwise of Group 2 automatically become Group 3 cases. Thus the large majority of the cases complicated with laryngeal tuberculosis are to be found in the two lower categories. Theoretically it would appear possible to re-classify all the patients so as to allow of a comparison being made between the Group 1 and Group 2 cases and those which would have qualified for these categories, save for the disease of the larynx. In practice, however, this procedure presents many difficulties. Actually the cases classified in Groups 2 and 3 under this section include many which, but for the disease of the larynx, would have been classified under Group 1 and Group 2.

Thus, the results now given, though indicating generally the influence of the factor of tuberculosis of the larynx, do not represent the extent to which the mortality of each group, as previously ascertained, is increased by the existence of this complication.

The number of cases which suffered from tuberculosis of the larynx was 319, of which 187 were males and 132 females.

Particulars as to medical classification and age group are given for both sexes in the following table:

TABLE XLVIII

Number of Patients with Tuberculosis of Larynx.

Age Group	Males				Females			
	Group 1	Group 2	Group 3	All Groups	Group 1	Group 2	Group 3	All Groups
-22	1	8	5	14	1	6	3	10
23-27	1	25	12	38	1	22	10	33
28-32	2	27	16	45	1	14	12	27
33-37	2	20	9	31	—	13	8	21
38-42	—	14	10	24	—	9	3	12
43-	—	15	20	35	1	11	17	29
Total	6	109	72	187	4	75	53	132
Percentage	3·2	58·3	38·5	100·0	3·0	56·8	40·2	100·0
All classes, percentage as per Table IV	27·4	51·4	21·2	100·0	26·2	46·9	26·9	100·0

It will be observed that the proportion of males and females are 58·6 per cent. and 41·4 per cent. respectively.

The variation of the numbers included in each group as compared with the whole body of patients is noticeable. For the reason already stated, only ten cases, six males and four females, are found in Group 1, or about 3 per cent., as compared with 27 per cent. in Table IV. Practically the whole of the difference is accounted for by the large number of cases found in Group 3, but a small percentage increase may be observed in Group 2. The proportions of cases of each sex in the three groups are, however, nearly the same.

The examination of Table XLVIII would seem to confirm the current impression that the infection of the larynx occurs generally as a complication in somewhat advanced pulmonary tuberculosis.

The mortality rates experienced by cases complicated with laryngeal disease may be seen from Table XLIX, which is an extract from the fuller Tables 42 and 43 in Appendix A.

TABLE XLIX

Ratios of Actual Deaths to Expected Deaths in Cases complicated with Tuberculosis of the Larynx.

	Group 1	Group 2	Group 3	All Groups
Males	5·2	26·8	50·4	32·4
Females	0 (4)[1]	29·0	30·8	27·4

The above clearly shows that cases complicated with disease of the larynx experience substantially higher rates of mortality than the other patients. The figures for Group 1, which show a ratio of 2·4 only, indicate that the relatively rare cases of early tuberculosis of the larynx associated with but slight disease of the lung enjoy quite a favourable prognosis. This conclusion is distinctly encouraging, but it is recognized that the data upon which it is founded are very scanty.

It remains to be added that the excess mortality of the cases of tuberculosis of the larynx is substantially heavier at the younger ages at discharge; in this respect these cases show the same features as cases classified under other categories.

CHAPTER VII

MORTALITY RATES AMONG PATIENTS WHO GAVE A FAMILY HISTORY OF TUBERCULOSIS.

As to how far there exists an inherited predisposition to tuberculosis is a somewhat vexed question. Powell and Hartley,[2] after summing the evidence bearing upon the point, conclude that 'In spite of what some modern critics may urge, the hereditary factor in consumption is one that cannot be gainsaid, and that it manifests itself in a special idiosyncrasy of the tissues in certain families and races whereby they become more than usually favourable to the growth of the tubercle bacillus'.

The data given in this section do not bear directly upon the issue of predisposition; they indicate rather how far, if at all, the prospects of recovery from pulmonary tuberculosis are prejudiced by the existence of a family history showing a predisposition to tuberculous disease.

To indicate what has been accepted as evidence of a family predisposition, the data in respect of every patient deemed to have a tuberculous family history have been summarized in the following Table L:

[1] 4 cases discharged, no deaths.

[2] *On Disease of the Lungs and Pleura.* Sir R. Douglas Powell, Bart., K.C.V.O., M.D., and P. Horton-Smith Hartley, C.V.O., M.D., 1911.

TABLE L

Table relative to 681 Patients who had a Family History of Tuberculosis.

The Incidence of the Disease among other Members of the Family.

Father or Mother or both	125
,, with Brothers or Sisters or both	71
,, with other relatives	27
Brothers and Sisters only	250
Brothers and Sisters with other relatives	39
Grandparents, Aunts and Uncles	168
Details of relationship not given	1
Total	681[1]

The number of cases under review which gave a family history as defined is 673, of which 351 or 52·2 per cent. are males and 322 or 47·8 per cent. females. The percentage of females who gave a family history is thus 49·2, a considerably higher figure than the 33·3 per cent. shown by the males. The explanation may be that the male patients, by the nature of their several occupations, were more exposed to risk of infection, so that although having no obvious predisposition to tuberculosis, they were more likely to contract the disease than the females, who for the most part were living at home.

Particulars of the 673 patients are given in Table LI, an inspection of which shows that the percentage of females in Groups 1 and 2 are less than for males, but is correspondingly greater in Group 3.

TABLE LI

Patients who presented a Family History of Tuberculosis.

Number of Males 351				Total 673	Number of Females 322			
Number of Patients in Group on Admission					Number of Patients in Group on Admission			
Group 1	Group 2	Group 3	All Groups	Age Group	Group 1	Group 2	Group 3	All Groups
15	21	7	43	-22	9	20	8	37
26	43	15	84	23-27	20	36	18	74
29	32	13	74	28-32	22	38	23	83
17	31	11	59	33-37	14	27	8	49
8	25	14	47	38-42	9	21	9	39
8	28	8	44	43-	7	22	11	40
103	180	68	351	Total	81	164	77	322
Percentage of Patients in Group on Admission				Age Group	Percentage of Patients in Group on Admission			
Group 1	Group 2	Group 3	All Groups		Group 1	Group 2	Group 3	All Groups
4·3	6·0	2·0	12·3	-22	2·8	6·2	2·5	11·5
7·4	12·2	4·3	23·9	23-27	6·2	11·2	5·6	23·0
8·2	9·1	3·7	21·0	28-32	6·8	11·8	7·1	25·7
4·8	8·9	3·1	16·8	33-37	4·4	8·4	2·5	15·3
2·3	7·1	4·0	13·4	38-42	2·8	6·5	2·8	12·1
2·3	8·0	2·3	12·6	43-	2·2	6·8	3·4	12·4
29·3	51·3	19·4	100·0	Total	25·2	50·9	23·9	100·0

[1] Of the 681 cases, 8 have been excluded from the investigation on account of the period of treatment being less than eight weeks.

Comparing the cases with a family history of tuberculosis with the body of patients without distinction, there is no outstanding variation apparent; certainly there are differences here and there, but generally speaking the distributions are similar. From a consideration of the age distribution it will be seen that the percentages of cases, male and female, which gave a positive history, occurring in each age group are also similar and that they closely correspond to those for the patients generally. Although there are proportionately a larger number of females than males, the incidence of the distribution of the cases in the three groups on admission as well as in the six age groups is nearly the same for the whole body as that for that section of it comprising only patients with a family history. The latter, it will have been noticed, consists of about 40 per cent. of the cases included in the former. It has already been pointed out that when making comparisons between various classifications, it is essential the data, as far as possible, be comparable. In this instance the essential condition obtains. The mortality of the patients who have a family history is set out in Table LII side by side with that of all the patients together; the latter is taken from Table V.

TABLE LII

Ratios of Actual Deaths to Expected Deaths:
(a) *those with a Family History of Tuberculosis, and*
(b) *those with and without such History.*

	Group 1		Group 2		Group 3		All Groups	
	Males	Females	Males	Females	Males	Females	Males	Females
(a)	7·5	4·2	15·5	18·0	40·4	41·1	15·9	17·5
(b)	6·4	4·7	15·6	19·0	39·2	37·5	15·7	18·2

The two sets of results are practically identical. The slight variations that exist are so trivial in character that they may be disregarded.

An analysis of the Adirondack experience in respect of family history showed a similar result, but in this instance only patients of whose parents one or both had suffered from consumption were included.

It would appear, therefore, that having contracted pulmonary tuberculosis, patients with a consumptive family history enjoy the same chance of recovery as those who have no such history. Also, it would seem that the patient's condition when admitted to a sanatorium is a more potent factor in prognosis than family antecedents.

An investigation undertaken a few years ago at the instance of the Prudential Assurance Company as to the mortality of healthy lives which gave a family history of consumption, disclosed results which support this conclusion.

As this work is of some interest in this connexion it is described in some detail in Appendix C.

PULMONARY TUBERCULOSIS.
MORTALITY AFTER SANATORIUM TREATMENT.

APPENDIX A

TABLE 1

Summary of Ratios of Actual Deaths to Expected Deaths.

MALES

Classification	Group 1	Group 2	Group 3	All Groups
All Conditions	6·4	15·6	39·2	15·7
Discharged Arrested	3·9	5·3	0 (2)	4·4
,, Much Improved	7·1	12·5	15·2	11·3
,, Improved	43·8	23·4	47·6	33·1
,, Worse	35·4	51·4	74·8	59·5
Tuberculin Control Years	9·5	15·7	—	13·6
Tuberculin Control Years (first 4 years only)	11·1	19·2	—	16·4
Tuberculin Years	7·2	17·1	—	15·5
Tuberculin Control Years (Selected Cases)	6·8	14·5	—	12·9
Tuberculin Control Years (Selected Cases, first 5 years only)	7·4	16·3	—	14·2
Cases treated with Tuberculin (1917)	12·1	16·2	—	15·4
Onset, Haemoptysis	5·1	11·6	30·0	11·4
,, Pleurisy	11·3	11·0	40·3	14·7
,, Insidious	6·1	18·5	42·5	17·9
Sputum, T. B. — —	3·7	9·6	11·6	5·5
,, T. B. + —	5·2	5·9	18·4	6·5
,, T. B. + +	8·8	19·9	44·2	21·8
Arrested, Sputum T. B. — —	2·6	—	—	—
Tuberculous Larynx	5·2	26·8	50·4	32·4
Tuberculous Family History	7·5	15·5	40·4	15·9

TABLE 2

Summary of Ratios of Actual Deaths to Expected Deaths.

FEMALES

Classification	Group 1	Group 2	Group 3	All Groups
All Conditions	4·7	19·0	37·5	18·2
Discharged Arrested	3·4	5·8	6·6	4·2
,, Much Improved	7·8	14·2	17·8	13·8
,, Improved	14·8	27·4	30·0	28·2
,, Worse	10·6	57·4	102·9	68·5
Tuberculin Control Years	11·3	24·5	—	21·5
Tuberculin Control Years (first 4 years only)	13·5	24·9	—	22·4
Tuberculin Years	11·8	28·4	—	25·6
Tuberculin Control Years (Selected Cases)	17·4	21·2	—	20·6
Tuberculin Control Years (Selected Cases, first 5 years only)	19·2	21·7	—	21·3
Cases treated with Tuberculin (1917)	8·5	21·1	—	18·6
Onset, Haemoptysis	4·5	12·5	47·0	14·7
,, Pleurisy	10·0	24·8	21·0	20·1
,, Insidious	4·1	19·6	39·7	18·7
Sputum, T. B. — —	2·5	4·2	0	3·1
,, T. B. + —	4·5	7·7	21·3	7·7
,, T. B. + +	11·8	29·6	39·9	31·6
Arrested, Sputum T. B. — —	2·8	—	—	—
Tuberculous Larynx	0 (4)	29·0	30·8	27·4
Tuberculous Family History	4·2	18·0	41·1	17·5

TABLE 3

Condition on Admission.

All Groups.

Males

Number of Patients Discharged 1,053

Duration since Discharge	Exposed to Risk	Lost Sight of	Existing	Actual Deaths	Expected Deaths	Ratio of Actual to Expected	Rate of Mortality
0 Years	1048	5	—	163	6·846	23·8	·15553
1 ,,	874	6	5	117	5·998	19·5	·13387
2 ,,	646	6	105	74	4·677	15·8	·11455
3 ,,	499	6	67	52	3·785	13·7	·10421
4 ,,	392	5	50	32	3·107	10·3	·08163
5 ,,	285	2	73	17	2·367	7·2	·05965
6 ,,	212	4	52	13	1·883	6·9	·06132
7 ,,	132	2	65	6	1·261	4·8	·04545
8 ,,	56	—	70	4	·554	7·2	·07143
9 ,,	—	—	52	—	—	—	—
Total	4144	36	539	478	30·478	15·7	·11535

Condition on Admission.

All Groups.

Females

Number of Patients Discharged 654

Duration since Discharge	Exposed to Risk	Lost Sight of	Existing	Actual Deaths	Expected Deaths	Ratio of Actual to Expected	Rate of Mortality
0 Years	651	3	—	82	3·259	25·2	·12596
1 ,,	564	5	—	73	2·936	24·9	·12943
2 ,,	426	4	61	53	2·305	23·0	·12441
3 ,,	325	2	46	31	1·844	16·8	·09538
4 ,,	253	2	39	14	1·536	9·1	·05534
5 ,,	186	6	47	15	1·226	12·2	·08065
6 ,,	136	2	33	3	·952	3·2	·02206
7 ,,	90	—	43	1	·609	1·6	·01111
8 ,,	44	—	45	1	·322	3·1	·02273
9 ,,	—	—	43	—	—	—	—
Total	2675	24	357	273	14·989	18·2	·10206

Condition on Admission.

All Groups.

Males and Females

Number of Patients Discharged 1,707

Duration since Discharge	Exposed to Risk	Lost Sight of	Existing	Actual Deaths	Expected Deaths	Ratio of Actual to Expected	Rate of Mortality
0 Years	1699	8	—	245	10·105	24·2	·14420
1 ,,	1438	11	5	190	8·934	21·3	·13212
2 ,,	1072	10	166	127	6·982	18·2	·11847
3 ,,	824	8	113	83	5·629	14·7	·10073
4 ,,	645	7	89	46	4·643	9·9	·07132
5 ,,	471	8	120	32	3·593	8·9	·06794
6 ,,	348	6	85	16	2·835	5·6	·04598
7 ,,	222	2	108	7	1·870	3·7	·03153
8 ,,	100	—	115	5	·876	5·7	·05000
9 ,,	—	—	95	—	—	—	—
Total	6819	60	896	751	45·467	16·5	·11013

TABLE 4

Condition on Admission.

Group 1.

MALES

Number of Patients Discharged 289

Duration since Discharge	Exposed to Risk	Lost Sight of	Existing	Actual Deaths	Expected Deaths	Ratio of Actual to Expected	Rate of Mortality
0 Years	288	1	—	10	1·724	5·8	·03472
1 ,,	275	3	—	12	1·760	6·8	·04364
2 ,,	231	2	30	11	1·599	6·9	·04762
3 ,,	205	1	14	14	1·467	9·5	·06829
4 ,,	170	4	17	10	1·275	7·8	·05882
5 ,,	123	—	37	6	·978	6·1	·04878
6 ,,	96	3	18	2	·841	2·4	·02083
7 ,,	58	2	34	2	·568	3·5	·03448
8 ,,	28	—	28	—	·307	—	—
9 ,,	—	—	28	—	—	—	—
Total	1474	16	206	67	10·519	6·4	·01545

Condition on Admission.

Group 2.

MALES

Number of Patients Discharged 541

Duration since Discharge	Exposed to Risk	Lost Sight of	Existing	Actual Deaths	Expected Deaths	Ratio of Actual to Expected	Rate of Mortality
0 Years	539	2	—	61	3·551	17·2	·11317
1 ,,	473	2	3	70	3·286	21·3	·14799
2 ,,	344	4	55	47	2·498	18·8	·13663
3 ,,	247	4	46	26	1·915	13·6	·10526
4 ,,	191	—	30	19	1·537	12·4	·09948
5 ,,	140	2	30	7	1·190	5·9	·05000
6 ,,	103	1	29	9	·920	9·8	·08738
7 ,,	65	—	29	3	·598	5·0	·04615
8 ,,	26	—	36	3	·231	13·0	·11538
9 ,,	—	—	23	—	—	—	—
Total	2128	15	281	245	15·726	15·6	·11513

Condition on Admission.

Group 3.

MALES

Number of Patients Discharged 223

Duration since Discharge	Exposed to Risk	Lost Sight of	Existing	Actual Deaths	Expected Deaths	Ratio of Actual to Expected	Rate of Mortality
0 Years	221	2	—	92	1·571	58·6	·41629
1 ,,	126	1	2	35	·952	36·8	·27778
2 ,,	71	—	20	16	·580	27·6	·22535
3 ,,	47	1	7	12	·403	29·8	·25532
4 ,,	31	1	3	3	·295	10·2	·09677
5 ,,	22	—	6	4	·199	20·1	·18182
6 ,,	13	—	5	2	·122	16·4	·15385
7 ,,	9	—	2	1	·095	10·5	·11111
8 ,,	2	—	6	1	·016	62·5	·50000
9 ,,	—	—	1	—	—	—	—
Total	542	5	52	166	4·233	39·2	·30627

TABLE 5

Condition on Admission.

Group 1.

FEMALES

Number of Patients Discharged 171

Duration since Discharge	Exposed to Risk	Lost Sight of	Existing	Actual Deaths	Expected Deaths	Ratio of Actual to Expected	Rate of Mortality
0 Years	171	—	—	3	·803	3·7	·01754
1 ,,	166	2	—	7	·822	8·5	·04217
2 ,,	142	—	17	4	·728	5·5	·02817
3 ,,	130	—	8	5	·704	7·1	·03846
4 ,,	107	1	17	1	·612	1·6	·00935
5 ,,	81	3	22	2	·495	4·0	·02469
6 ,,	61	1	17	1	·399	2·5	·01639
7 ,,	37	—	23	—	·219	—	—
8 ,,	21	—	16	—	·133	—	—
9 ,,	—	—	21	—	—	—	—
Total	916	7	141	23	4·915	4·7	·02511

Condition on Admission.

Group 2.

FEMALES

Number of Patients Discharged 307

Duration since Discharge	Exposed to Risk	Lost Sight of	Existing	Actual Deaths	Expected Deaths	Ratio of Actual to Expected	Rate of Mortality
0 Years	305	2	—	23	1·557	14·8	·07541
1 ,,	279	3	—	34	1·480	23·0	·12186
2 ,,	207	4	34	34	1·118	30·4	·16425
3 ,,	145	2	26	21	·837	25·1	·14483
4 ,,	105	1	18	10	·658	15·2	·09524
5 ,,	74	3	18	7	·504	13·9	·09459
6 ,,	53	—	14	1	·370	2·7	·01887
7 ,,	37	—	15	1	·255	3·9	·02703
8 ,,	15	—	21	—	·120	—	—
9 ,,	—	—	15	—	—	—	—
Total	1220	15	161	131	6·899	19·0	·10738

Condition on Admission.

Group 3.

FEMALES

Number of Patients Discharged 176

Duration since Discharge	Exposed to Risk	Lost Sight of	Existing	Actual Deaths	Expected Deaths	Ratio of Actual to Expected	Rate of Mortality
0 Years	175	1	—	56	·899	62·3	·32000
1 ,,	119	—	—	32	·634	50·5	·26891
2 ,,	77	—	10	15	·459	32·7	·19481
3 ,,	50	—	12	5	·303	16·5	·10000
4 ,,	41	—	4	3	·266	11·3	·07317
5 ,,	31	—	7	6	·227	26·4	·19355
6 ,,	22	1	2	1	·183	5·5	·04545
7 ,,	16	—	5	—	·135	—	—
8 ,,	8	—	8	1	·069	14·5	·12500
9 ,,	—	—	7	—	—	—	—
Total	539	2	55	119	3·175	37·5	·22078

TABLE 6

Condition on Admission.

All Groups.

MALES

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected	Rate of Mortality
-22	127	505	49	1·896	25·8	·09703
23-27	249	991	113	4·301	26·3	·11403
28-32	219	863	97	4·661	20·8	·11240
33-37	185	780	89	5·557	16·0	·11410
38-42	120	422	64	3·905	16·4	·15166
43-	153	583	66	10·158	6·5	·11321
Total	1053	4144	478	30·478	15·7	·11535

All Groups.

FEMALES

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected	Rate of Mortality
-22	77	306	39	·971	40·2	·12745
23-27	166	673	70	2·493	28·1	·10401
28-32	157	670	63	3·004	20·4	·09403
33-37	107	456	42	2·683	15·6	·09211
38-42	70	277	34	2·050	16·6	·12274
43-	77	293	25	3·698	6·8	·08532
Total	654	2675	273	14·989	18·2	·10206

TABLE 7

MALES

Condition on Admission.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	48	214	12	·803	14·9
23-27	72	373	16	1·646	9·7
28-32	69	347	19	1·908	10·0
33-37	47	253	14	1·833	7·6
38-42	20	104	3	·996	3·0
43-	33	183	3	3·331	·9
Total	289	1474	67	10·519	6·4

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	61	246	25	·923	27·1
23-27	124	501	55	2·167	25·4
28-32	106	396	47	2·125	22·1
33-37	99	432	45	3·074	14·6
38-42	76	263	41	2·432	16·9
43-	75	290	32	5·005	6·4
Total	541	2128	245	15·726	15·6

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	18	45	12	·168	71·4
23-27	53	117	42	·488	86·1
28-32	44	120	31	·628	49·4
33-37	39	95	30	·650	46·2
38-42	24	55	20	·477	41·9
43-	45	110	31	1·822	17·0
Total	223	542	166	4·233	39·2

TABLE 8

Females

Condition on Admission.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	20	114	2	·369	5·4
23-27	46	229	6	·855	7·0
28-32	50	279	7	1·317	5·3
33-37	28	152	4	·907	4·4
38-42	13	68	4	·516	7·8
43-	14	74	—	·951	—
Total	171	916	23	4·915	4·7

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	33	129	17	·406	41·9
23-27	81	318	39	1·173	33·2
28-32	61	241	27	1·096	24·6
33-37	55	238	21	1·397	15·0
38-42	40	165	17	1·222	13·9
43-	37	129	10	1·605	6·2
Total	307	1220	131	6·899	19·0

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	24	63	20	·196	102·0
23-27	39	126	25	·465	53·8
28-32	46	150	29	·681	42·6
33-37	24	66	17	·379	44·9
38-42	17	44	13	·312	41·7
43-	26	90	15	1·142	13·1
Total	176	539	119	3·175	37·5

TABLE 9

Males

Condition on Discharge. Arrested.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	26	133	4	·503	8·0
23-27	47	249	7	1·099	6·4
28-32	39	220	5	1·222	4·1
33-37	26	141	5	1·018	4·9
38-42	10	64	1	·626	1·6
43-	13	79	1	1·468	·7
Total	161	886	23	5·936	3·9

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	12	69	2	·262	7·6
23-27	28	133	5	·574	8·7
28-32	20	97	2	·523	3·8
33-37	19	92	4	·653	6·1
38-42	10	40	2	·375	5·3
43-	15	59	3	1·010	3·0
Total	104	490	18	3·397	5·3

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	1	8	—	·031	—
23-27	—	—	—	—	—
28-32	—	—	—	—	—
33-37	1	7	—	·052	—
38-42	—	—	—	—	—
43-	—	—	—	—	—
Total	2	15	—	·083	—

TABLE 10

Females

Condition on Discharge. Arrested.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	16	101	1	·329	3·0
23-27	32	165	3	·618	4·9
28-32	35	208	5	·988	5·1
33-37	20	116	3	·696	4·3
38-42	8	49	1	·378	2·6
43-	11	63	—	·814	—
Total	122	702	13	3·823	3·4

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	8	42	2	·135	14·8
23-27	15	66	4	·243	16·5
28-32	7	42	1	·199	5·0
33-37	11	59	—	·354	—
38-42	6	32	1	·246	4·1
43-	8	30	1	·363	2·8
Total	55	271	9	1·540	5·8

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	1	3	—	·009	—
23-27	1	8	—	·032	—
28-32	—	—	—	—	—
33-37	—	—	—	—	—
38-42	—	—	—	—	—
43-	2	9	1	·110	9·1
Total	4	20	1	·151	6·6

TABLE 11

Males

Condition on Discharge. Much Improved.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	15	57	4	·213	18·8
23-27	23	112	8	·494	16·2
28-32	22	109	6	·598	10·0
33-37	20	110	8	·800	10·0
38-42	9	38	2	·353	5·7
43-	18	98	2	1·769	1·1
Total	107	524	30	4·227	7·1

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	25	108	10	·409	24·4
23-27	52	224	18	·976	18·5
28-32	50	195	19	1·056	18·0
33-37	66	293	29	2·093	13·9
38-42	41	159	19	1·491	12·7
43-	36	158	15	2·767	5·4
Total	270	1137	110	8·792	12·5

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	4	19	2	·072	27·8
23-27	10	25	6	·105	57·1
28-32	16	63	7	·333	21·0
33-37	9	39	4	·281	14·2
38-42	3	7	2	·060	33·3
43-	15	54	6	·931	6·4
Total	57	207	27	1·782	15·2

TABLE 12

Females

Condition on Discharge. Much Improved.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	3	12	—	·036	—
23-27	12	52	3	·190	15·8
28-32	11	56	1	·262	3·8
33-37	7	33	1	·199	5·0
38-42	2	6	1	·042	23·8
43-	2	4	—	·044	—
Total	37	163	6	·773	7·8

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	12	40	6	·125	48·0
23-27	32	145	14	·543	25·8
28-32	26	113	8	·517	15·5
33-37	25	105	11	·618	17·8
38-42	17	83	7	·621	11·3
43-	14	68	1	·876	1·1
Total	126	554	47	3·300	14·2

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	2	6	1	·018	55·6
23-27	7	39	2	·149	13·4
28-32	12	47	5	·212	23·6
33-37	4	8	2	·043	46·5
38-42	5	22	2	·162	12·3
43-	5	20	3	·258	11·6
Total	35	142	15	·842	17·8

TABLE 13

Males

Condition on Discharge. Improved.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	2	4	1	·015	66·7
23-27	2	12	1	·053	18·9
28-32	5	9	5	·044	113·6
33-37	—	—	—	—	—
38-42	—	—	—	—	—
43-	1	3	—	·048	—
Total	10	28	7	·160	43·8

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	9	27	5	·099	50·5
23-27	24	101	14	·439	31·9
28-32	18	60	12	·322	37·3
33-37	6	27	6	·190	31·6
38-42	12	36	9	·325	27·7
43-	16	55	8	·930	8·6
Total	85	306	54	2·305	23·4

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	6	7	4	·025	160·0
23-27	25	57	23	·240	95·8
28-32	11	25	10	·134	74·6
33-37	11	23	9	·153	58·8
38-42	9	25	7	·222	31·5
43-	17	39	14	·633	22·1
Total	79	176	67	1·407	47·6

TABLE 14

Females

Condition on Discharge. Improved.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	—	—	—	—	—
23-27	1	9	—	·037	—
28-32	2	9	—	·040	—
33-37	1	3	—	·016	—
38-42	2	6	2	·042	47·6
43-	—	—	—	—	—
Total	6	27	2	·135	14·8

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	7	25	5	·079	63·3
23-27	23	84	14	·306	45·8
28-32	14	51	7	·232	30·2
33-37	12	54	5	·318	15·7
38-42	11	37	6	·267	22·5
43-	8	21	3	·256	11·7
Total	75	272	40	1·458	27·4

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	14	40	13	·126	103·2
23-27	16	55	9	·202	44·6
28-32	19	83	10	·384	26·0
33-37	11	41	8	·243	32·9
38-42	4	12	4	·084	47·6
43-	11	48	6	·628	9·6
Total	75	279	50	1·667	30·0

TABLE 15

Males

Condition on Discharge. Worse.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	5	20	3	·074	40·5
23-27	—	—	—	—	—
28-32	3	9	3	·046	65·2
33-37	1	2	1	·013	76·9
38-42	1	2	—	·017	—
43-	1	3	—	·048	—
Total	11	36	7	·198	35·4

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	15	42	8	·153	52·3
23-27	20	43	18	·177	101·7
28-32	18	44	14	·222	63·1
33-37	8	20	6	·137	43·8
38-42	13	28	11	·240	45·8
43-	8	18	6	·297	20·2
Total	82	195	63	1·226	51·4

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	7	11	6	·039	153·8
23-27	18	35	13	·145	89·7
28-32	17	32	14	·161	87·0
33-37	18	26	17	·166	102·4
38-42	12	23	11	·193	57·0
43-	13	17	11	·258	42·6
Total	85	144	72	·962	74·8

TABLE 16

Females

Condition on Discharge. Worse.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	1	1	1	·003	333·3
23-27	1	3	—	·011	—
28-32	2	6	1	·027	37·0
33-37	—	—	—	—	—
38-42	1	7	—	·055	—
43-	1	7	—	·092	—
Total	6	24	2	·188	10.6

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	6	22	4	·069	58·0
23-27	11	23	7	·080	87·5
28-32	14	35	11	·152	72·4
33-37	7	20	5	·110	45·5
38-42	6	13	3	·090	33·3
43-	7	10	5	·109	45·9
Total	51	123	35	·610	57·4

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	7	14	6	·042	142·9
23-27	15	24	14	·083	168·7
28-32	15	20	14	·084	166·7
33-37	9	17	7	·093	75·2
38-42	8	10	7	·067	104·5
43-	8	13	5	·146	34·2
Total	62	98	53	·515	102·9

TABLE 17

Males

Tuberculin Control Years 1908, 1910, *and* 1911.

Groups 1 and 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	29	133	15	·500	30·0
23-27	60	291	31	1·268	24·4
28-32	57	246	28	1·320	21·2
33-37	50	261	17	1·879	9·0
38-42	26	108	14	1·010	13·9
43-	31	149	12	2·631	4·6
Total	253	1188	117	8·608	13·6

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	11	47	6	·177	33·9
23-27	15	86	6	·378	15·9
28-32	26	121	11	·650	15·4
33-37	12	65	2	·467	4·3
38-42	4	22	1	·208	4·8
43-	11	60	2	1·068	1·9
Total	79	401	28	2·948	9·5

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	18	86	9	·323	27·9
23-27	45	205	25	·890	28·1
28-32	31	125	17	·670	25·4
33-37	38	196	15	1·412	10·6
38-42	22	86	13	·802	16·2
43-	20	89	10	1·563	6·4
Total	174	787	89	5·660	15·7

TABLE 18

Females

Tuberculin Control Years 1908, 1910, *and* 1911.

Groups 1 and 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	13	62	5	·193	25·9
23-27	36	169	17	·626	27·2
28-32	27	120	12	·549	21·9
33-37	21	97	11	·571	19·3
38-42	16	72	12	·529	22·7
43-	7	26	3	·319	9·4
Total	120	546	60	2·787	21·5

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	1	6	—	·018	—
23-27	10	53	3	·198	15·2
28-32	9	47	1	·217	4·7
33-37	1	8	—	·049	—
38-42	3	11	3	·078	38·5
43-	1	5	—	·061	—
Total	25	130	7	·621	11·3

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	12	56	5	·175	28·6
23-27	26	116	14	·428	32·7
28-32	18	73	11	·332	33·1
33-37	20	89	11	·522	21·1
38-42	13	61	9	·451	20·0
43-	6	21	3	·258	11·6
Total	95	416	53	2·166	24·5

TABLE 19

Males

Tuberculin Control Years 1908, 1910, *and* 1911.

First Four Years' Experience Only

Groups 1 and 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	29	98	14	·359	39·0
23-27	60	204	23	·851	27·0
28-32	57	185	22	·946	23·3
33-37	50	178	13	1·199	10·8
38-42	26	76	13	·660	19·7
43-	31	108	10	1·766	5·7
Total	253	849	95	5·781	16·4

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	11	35	6	·128	46·9
23-27	15	57	3	·239	12·6
28-32	26	90	8	·461	17·4
33-37	12	46	2	·310	6·5
38-42	4	15	1	·131	7·6
43-	11	43	2	·707	2·8
Total	79	286	22	1·976	11·1

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	18	63	8	·231	34·6
23-27	45	147	20	·612	32·7
28-32	31	95	14	·485	28·9
33-37	38	132	11	·889	12·4
38-42	22	61	12	·529	22·7
43-	20	65	8	1·059	7·6
Total	174	563	73	3·805	19·2

TABLE 20

Females

Tuberculin Control Years 1908, 1910, *and* 1911.

First Four Years' Experience Only

Groups 1 and 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	13	45	4	·137	29·2
23-27	36	126	14	·449	31·2
28-32	27	92	9	·405	22·2
33-37	21	68	8	·378	21·2
38-42	16	58	8	·411	19·5
43-	7	20	2	·233	8·6
Total	120	409	45	2·013	22·4

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	1	4	—	·012	—
23-27	10	38	2	·136	14·7
28-32	9	34	1	·150	6·7
33-37	1	4	—	·022	—
38-42	3	11	3	·078	38·5
43-	1	4	—	·047	—
Total	25	95	6	·445	13·5

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	12	41	4	·125	32·0
23-27	26	88	12	·313	38·3
28-32	18	58	8	·255	31·4
33-37	20	64	8	·356	22·5
38-42	13	47	5	·333	15·0
43-	6	16	2	·186	10·8
Total	95	314	39	1·568	24·9

TABLE 21

Males

Tuberculin Years 1912, 1913, *and* 1914.

Groups 1 and 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	27	67	3	·247	12·1
23-27	50	131	12	·538	22·3
28-32	49	123	12	·616	19·5
33-37	33	83	15	·545	27·5
38-42	38	89	15	·759	19·8
43-	37	102	10	1·625	6·2
Total	234	595	67	4·330	15·5

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	7	17	—	·066	—
23-27	11	28	1	·115	8·7
28-32	10	25	2	·125	16·0
33-37	3	8	2	·052	38·5
38-42	6	15	—	·128	—
43-	4	13	—	·209	—
Total	41	106	5	·695	7·2

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	20	50	3	·181	16·6
23-27	39	103	11	·423	26·0
28-32	39	98	10	·491	20·4
33-37	30	75	13	·493	26·4
38-42	32	74	15	·631	23·8
43-	33	89	10	1·416	7·1
Total	193	489	62	3·635	17·1

TABLE 22

Females

Tuberculin Years 1912, 1913, *and* 1914.

Groups 1 and 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	13	32	7	·096	72·9
23-27	29	80	11	·282	39·0
28-32	22	55	7	·283	24·7
33-37	17	40	5	·217	23·0
38-42	11	23	4	·157	25·5
43-	17	40	4	·451	8·9
Total	109	270	38	1·486	25·6

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	2	5	1	·015	66·7
23-27	6	20	—	·070	—
28-32	2	8	—	·035	—
33-37	4	8	2	·043	46·5
38-42	—	—	—	—	—
43-	3	8	—	·091	—
Total	17	49	3	·254	11·8

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	11	27	6	·081	74·1
23-27	23	60	11	·212	51·9
28-32	20	47	7	·248	28·2
33-37	13	32	3	·174	17·2
38-42	11	23	4	·157	25·5
43-	14	32	4	·360	11·1
Total	92	221	35	1·232	28·4

TABLE 23

Males

Tuberculin Control Years 1908, 1910 *and* 1911.

Selected Cases.[1]

Groups 1 and 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	19	83	9	·313	28·8
23-27	48	234	24	1·019	23·6
28-32	34	142	16	·758	21·1
33-37	32	166	10	1·181	8·5
38-42	14	74	4	·709	5·6
43-	21	89	8	1·541	5·2
Total	168	788	71	5·521	12·9

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	6	20	3	·075	40·0
23-27	7	43	1	·191	5·2
28-32	9	44	2	·236	8·5
33-37	4	15	1	·102	9·8
38-42	2	13	—	·125	—
43-	6	27	1	·456	2·2
Total	34	162	8	1·185	6·8

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	13	63	6	·238	25·2
23-27	41	191	23	·828	27·8
28-32	25	98	14	·522	26·8
33-37	28	151	9	1·079	8·3
38-42	12	61	4	·584	6·8
43-	15	62	7	1·085	6·5
Total	134	626	63	4·336	14·5

[1] In this classification no cases have been excluded on account of the period of treatment at the sanatorium being less than eight weeks.

TABLE 24

Females

Tuberculin Control Years 1908, 1910, *and* 1911.

Selected Cases.[1]

Groups 1 and 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	4	16	2	·049	40·8
23-27	20	98	8	·364	22·0
28-32	16	80	6	·371	16·2
33-37	15	66	9	·387	23·3
38-42	9	39	7	·288	24·3
43-	6	20	3	·243	12·3
Total	70	319	35	1·702	20·6

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	—	—	—	—	—
23-27	5	22	2	·081	24·7
28-32	6	32	1	·150	6·7
33-37	—	—	—	—	—
38-42	2	8	2	·057	35·1
43-	—	—	—	—	—
Total	13	62	5	·288	17·4

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	4	16	2	·049	40·8
23-27	15	76	6	·283	21·2
28-32	10	48	5	·221	22·6
33-37	15	66	9	·387	23·3
38-42	7	31	5	·231	21·6
43-	6	20	3	·243	12·3
Total	57	257	30	1·414	21·2

[1] In this classification no cases have been excluded on account of the period of treatment at the sanatorium being less than eight weeks.

TABLE 25

Males

Tuberculin Control Years 1908, 1910. *and* 1911.

Selected Cases.[1]

First Five Years' Experience Only

Groups 1 and 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	19	70	9	·260	34·6
23–27	48	193	22	·816	27·0
28–32	34	132	15	·693	21·6
33–37	32	143	8	·988	8·1
38–42	14	57	4	·514	7·8
43–	21	81	8	1·363	5·9
Total	168	676	66	4·634	14·2

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	6	19	3	·071	42·3
23–27	7	33	1	·141	7·1
28–32	9	41	2	·217	9·2
33–37	4	15	1	·102	9·8
38–42	2	10	—	·090	—
43–	6	27	1	·456	2·2
Total	34	145	8	1·077	7·4

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	13	51	6	·189	31·7
23–27	41	160	21	·675	31·1
28–32	25	91	13	·476	27·3
33–37	28	128	7	·886	7·9
38–42	12	47	4	·424	9·4
43–	15	54	7	·907	7·7
Total	134	531	58	3·557	16·3

[1] In this classification no cases have been excluded on account of the period of treatment at the sanatorium being less than eight weeks.

TABLE 26

Females

Tuberculin Control Years 1908, 1910. *and* 1911.

Selected Cases.[1]

First Five Years' Experience Only

Groups 1 and 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	4	15	2	·046	43·5
23-27	20	87	8	·316	25·3
28-32	16	69	6	·312	19·2
33-37	15	54	7	·304	23·0
38-42	9	35	6	·252	23·8
43-	6	19	2	·228	8·8
Total	70	279	31	1·458	21·3

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	—	—	—	—	—
23-27	5	22	2	·081	24·7
28-32	6	27	1	·123	8·1
33-37	—	—	—	—	—
38-42	2	8	2	·057	35·1
43-	—	—	—	—	—
Total	13	57	5	·261	19·2

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	4	15	2	·046	43·5
23-27	15	65	6	·235	25·5
28-32	10	42	5	·189	26·5
33-37	15	54	7	·304	23·0
38-42	7	27	4	·195	20·5
43-	6	19	2	·228	8·8
Total	57	222	26	1·197	21·7

[1] In this classification no cases have been excluded on account of the period of treatment at the sanatorium being less than eight weeks.

TABLE 27

Males

Cases treated with Tuberculin during Tuberculin Years 1912, 1913, *and* 1914.[1]

Observations Extended to Anniversary of Discharge in 1917

Groups 1 and 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	17	53	3	·194	15·5
23-27	35	120	10	·501	20·0
28-32	43	144	16	·738	21·7
33-37	24	76	9	·507	17·8
38-42	29	83	13	·721	18·0
43-	20	68	7	1·115	6·3
Total	168	544	58	3·776	15·4

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	6	17	2	·062	32·3
23-27	8	29	1	·122	8·2
28-32	9	29	4	·148	27·0
33-37	2	6	2	·039	51·3
38-42	6	20	—	·175	—
43-	3	12	—	·200	—
Total	34	113	9	·746	12·1

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	11	36	1	·132	7·6
23-27	27	91	9	·379	23·7
28-32	34	115	12	·590	20·3
33-37	22	70	7	·468	15·0
38-42	23	63	13	·546	23·8
43-	17	56	7	·915	7·7
Total	134	431	49	3·030	16·2

[1] In this classification no cases have been excluded on account of the period of treatment at the sanatorium being less than eight weeks.

TABLE 28

Females

Cases treated with Tuberculin during Tuberculin Years 1912, 1913, *and* 1914.[1]

Observations Extended to Anniversary of Discharge in 1917.

Groups 1 and 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	9	26	5	·080	62·5
23-27	20	66	7	·235	29·8
28-32	16	64	3	·284	10·6
33-37	12	35	5	·193	25·9
38-42	6	16	2	·111	18·0
43-	7	24	—	·279	—
Total	70	231	22	1·182	18·6

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	1	5	—	·015	—
23-27	6	25	—	·090	—
28-32	2	10	—	·045	—
33-37	3	7	2	·039	51·3
38-42	—	—	—	—	—
43-	1	4	—	·047	—
Total	13	51	2	·236	8·5

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	8	21	5	·065	76·9
23-27	14	41	7	·145	48·3
28-32	14	54	3	·239	12·6
33-37	9	28	3	·154	19·5
38-42	6	16	2	·111	18·0
43-	6	20	—	·232	—
Total	57	180	20	·946	21·1

[1] In this classification no cases have been excluded on account of the period of treatment at the sanatorium being less than eight weeks.

TABLE 29

Males

Type of Onset—Haemoptysis.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	16	72	3	·270	11·1
23-27	24	120	3	·530	5·7
28-32	24	111	6	·611	9·8
33-37	12	63	4	·458	8·7
38-42	6	35	—	·340	—
43-	7	49	—	·922	—
Total	89	450	16	3·131	5·1

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	12	57	5	·217	23·0
23-27	26	138	4	·608	6·6
28-32	27	88	13	·460	28·3
33-37	31	132	11	·936	11·8
38-42	21	84	8	·793	10·1
43-	19	79	10	1·385	7·2
Total	136	578	51	4·399	11·6

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	7	28	5	·107	46·7
23-27	8	17	7	·071	98·6
28-32	8	28	5	·148	33·8
33-37	5	8	5	·051	98·0
38-42	3	5	3	·041	73·2
43-	10	36	6	·615	9·8
Total	41	122	31	1·033	30·0

TABLE 30

Females

Type of Onset—Haemoptysis.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	5	24	—	·078	—
23-27	7	25	1	·091	11·0
28-32	7	38	1	·177	5·6
33-37	6	34	1	·205	4·9
38-42	3	18	1	·138	7·2
43-	3	16	—	·206	—
Total	31	155	4	·895	4·5

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	3	22	—	·072	—
23-27	12	51	4	·189	21·2
28-32	10	44	4	·204	19·6
33-37	11	54	3	·321	9·4
38-42	8	31	4	·232	17·2
43-	4	15	—	·180	—
Total	48	217	15	1·198	12·5

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	4	13	2	·039	51·3
23-27	3	9	3	·033	90·9
28-32	6	18	4	·081	49·4
33-37	6	15	3	·084	35·7
38-42	3	4	3	·027	111·1
43-	3	8	2	·098	20·4
Total	25	67	17	·362	47·0

TABLE 31

Males

Type of Onset—Pleurisy.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	4	12	3	·044	68·2
23-27	7	43	4	·190	21·1
28-32	8	37	2	·203	9·9
33-37	8	47	3	·345	8·7
38-42	3	11	1	·097	10·3
43-	4	16	—	·274	—
Total	34	166	13	1·153	11·3

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	9	30	4	·111	36·0
23-27	8	45	2	·201	10·0
28-32	15	70	4	·380	10·5
33-37	13	59	5	·423	11·8
38-42	10	33	5	·311	16·1
43-	6	32	2	·582	3·4
Total	61	269	22	2·008	11·0

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	2	2	1	·007	142·9
23-27	6	13	5	·054	92·6
28-32	4	15	3	·079	38·0
33-37	8	17	7	·114	61·4
38-42	1	1	1	·008	125·0
43-	3	11	1	·185	5·4
Total	24	59	18	·447	40·3

TABLE 32

Females

Type of Onset—Pleurisy.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	3	25	—	·083	—
23-27	7	35	2	·129	15·5
28-32	4	24	—	·116	—
33-37	4	13	2	·074	27·0
38-42	—	—	—	—	—
43-	—	—	—	—	—
Total	18	97	4	·402	10·0

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	3	7	2	·021	95·2
23-27	14	52	6	·193	31·1
28-32	6	11	5	·047	106·4
33-37	7	27	5	·157	31·8
38-42	3	16	—	·122	—
43-	4	18	1	·226	4·4
Total	37	131	19	·766	24·8

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	2	12	1	·039	25·6
23-27	7	31	3	·117	25·6
28-32	6	19	3	·084	35·7
33-37	3	11	2	·063	31·7
38-42	—	—	—	—	—
43-	2	16	2	·220	9·1
Total	20	89	11	·523	21·0

TABLE 33

Males

Type of Onset—Insidious.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	28	130	6	·491	12·2
23-27	41	210	9	·926	9·7
28-32	37	199	11	1·098	10·0
33-37	27	143	7	1·031	6·8
38-42	11	58	2	·556	3·6
43-	22	118	3	2·137	1·4
Total	166	858	38	6·239	6·1

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	40	159	16	·596	26·8
23-27	90	318	49	1·359	36·1
28-32	64	238	30	1·283	23·4
33-37	55	241	29	1·712	16·9
38-42	45	146	28	1·327	21·1
43-	50	179	20	3·038	6·6
Total	344	1281	172	9·315	18·5

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	9	15	6	·053	113·2
23-27	39	87	30	·364	82·4
28-32	32	77	23	·402	57·2
33-37	26	70	18	·485	37·1
38-42	20	49	16	·427	37·5
43-	32	63	24	1·021	23·5
Total	158	361	117	2·752	42·5

TABLE 34

Females

Type of Onset—Insidious.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	12	65	2	·208	9·6
23-27	32	169	3	·635	4·7
28-32	39	217	6	1·023	5·9
33-37	18	105	1	·631	1·6
38-42	10	50	3	·378	7·9
43-	11	58	—	·744	—
Total	122	664	15	3·619	4·1

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	27	100	15	·313	47·9
23-27	55	215	29	·792	36·6
28-32	45	186	18	·849	21·2
33-37	37	157	13	·921	14·1
38-42	29	118	13	·868	15·0
43-	29	96	9	1·200	7·5
Total	222	872	97	4·943	19·6

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	18	38	17	·116	146·6
23-27	29	86	19	·317	59·9
28-32	34	113	22	·516	42·6
33-37	15	40	12	·232	51·7
38-42	14	40	10	·285	35·1
43-	21	66	11	·824	13·3
Total	131	383	91	2·290	39·7

TABLE 35

Males

Sputum, T. B. — —.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	16	83	2	·315	6·3
23-27	15	87	2	·388	5·2
28-32	11	69	1	·387	2·6
33-37	12	53	3	·377	8·0
38-42	3	18	—	·171	—
43-	8	43	1	·787	1·3
Total	65	353	9	2·425	3·7

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	5	27	2	·102	19·6
23-27	7	35	2	·153	13·1
28-32	4	16	1	·085	11·8
33-37	5	17	2	·114	17·5
38-42	3	11	1	·098	10·2
43-	2	15	—	·283	—
Total	26	121	8	·835	9·6

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	—	—	—	—	—
23-27	1	1	1	·004	250·0
28-32	1	4	1	·021	47·6
33-37	1	7	—	·052	—
38-42	—	—	—	—	—
43-	2	6	—	·096	—
Total	5	18	2	·173	11·6

TABLE 36

Females

Sputum, T. B. — —.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	10	69	1	·224	4·5
23-27	17	75	1	·279	3·6
28-32	23	134	2	·634	3·2
33-37	15	85	2	·506	4·0
38-42	7	46	—	·357	—
43-	6	31	—	·391	—
Total	78	440	6	2·391	2·5

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	2	9	1	·029	34·5
23-27	6	14	2	·048	41·7
28-32	3	23	—	·112	—
33-37	9	54	—	·327	—
38-42	6	29	1	·219	4·6
43-	7	36	1	·468	2·1
Total	33	165	5	1·203	4·2

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	—	—	—	—	—
23-27	—	—	—	—	—
28-32	—	—	—	—	—
33-37	—	—	—	—	—
38-42	—	—	—	—	—
43-	1	—	—	—	—
Total	1	—	—	—	—

TABLE 37

Males

Sputum, T. B. + —.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	15	61	2	·227	8·8
23-27	34	176	6	·774	7·8
28-32	30	157	6	·867	6·9
33-37	17	92	4	·664	6·0
38-42	7	46	1	·455	2·2
43-	8	38	—	·685	—
Total	111	570	19	3·672	5·2

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	12	66	1	·252	4·0
23-27	34	159	8	·691	11·6
28-32	24	116	3	·635	4·7
33-37	26	116	6	·825	7·3
38-42	14	67	3	·649	4·6
43-	18	70	4	1·203	3·3
Total	128	594	25	4·255	5·9

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	2	9	—	·035	—
23-27	4	18	4	·081	49·4
28-32	2	7	—	·037	—
33-37	2	8	1	·055	18·2
38-42	1	1	1	·008	125·0
43-	6	22	5	·382	13·1
Total	17	65	11	·598	18·4

TABLE 38

Females

Sputum, T. B. + —.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	7	34	—	·110	—
23-27	19	102	2	·384	5·2
28-32	19	100	4	·471	8·5
33-37	9	45	1	·270	3·7
38-42	3	12	1	·090	11·1
43-	6	34	—	·443	—
Total	63	327	8	1·768	4·5

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	11	42	5	·132	37·9
23-27	20	88	3	·327	9·2
28-32	14	63	3	·290	10·3
33-37	13	67	3	·399	7·5
38-42	7	38	1	·288	3·5
43-	9	40	—	·507	—
Total	74	338	15	1·943	7·7

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	4	12	2	·036	55·6
23-27	3	12	2	·045	44·4
28-32	6	24	2	·108	18·5
33-37	3	6	2	·033	60·6
38-42	1	7	—	·055	—
43-	3	12	1	·145	6·9
Total	20	73	9	·422	21·3

TABLE 39

Males

Sputum, T. B. + +.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	17	70	8	·262	30·5
23-27	23	110	8	·484	16·5
28-32	28	121	12	·658	18·2
33-37	18	108	7	·791	8·8
38-42	10	40	2	·370	5·4
43-	17	102	2	1·861	1·1
Total	113	551	39	4·426	8·8

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	44	153	22	·569	38·7
23-27	83	307	45	1·323	34·0
28-32	78	264	43	1·406	30·6
33-37	68	299	37	2·131	17·4
38-42	59	185	37	1·684	22·0
43-	55	205	28	3·519	8·0
Total	387	1413	212	10·632	19·9

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	16	36	12	·132	90·9
23-27	48	98	37	·404	91·6
28-32	41	109	30	·570	52·6
33-37	36	80	29	·544	53·3
38-42	23	54	19	·469	40·5
43-	37	82	26	1·344	19·3
Total	201	459	153	3·463	44·2

TABLE 40

Females

Sputum, T. B. + +.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	3	11	1	·034	29·4
23-27	10	52	3	·195	15·4
28-32	8	45	1	·213	4·7
33-37	4	22	1	·135	7·4
38-42	3	10	3	·071	42·3
43-	2	9	—	·114	—
Total	30	149	9	·762	11·8

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	20	78	11	·244	45·1
23-27	55	216	34	·798	42·6
28-32	44	155	24	·696	34·5
33-37	33	117	18	·671	26·8
38-42	27	98	15	·716	20·9
43-	21	53	9	·629	14·3
Total	200	717	111	3·754	29·6

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	20	51	18	·160	112·5
23-27	36	114	23	·420	54·8
28-32	40	126	27	·573	47·1
33-37	21	60	15	·346	43·4
38-42	16	37	13	·258	50·4
43-	22	78	14	·998	14·0
Total	155	466	110	2·755	39·9

TABLE 41

Condition on Admission. Group 1, Sputum T. B. —.
Condition on Discharge. Arrested, Sputum T. B. —.

Males

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	13	70	2	·264	7·6
23 27	14	80	2	·356	5·6
28-32	10	68	—	·382	—
33-37	10	50	1	·358	2·8
38-42	3	18	—	·171	—
43-	7	41	1	·756	1·3
Total	57	327	6	2·287	2·6

Females

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	9	67	1	·218	4·6
23-27	14	66	1	·248	4·0
28-32	19	118	2	·562	3·6
33-37	13	75	2	·447	4·5
38-42	6	39	—	·303	—
43-	5	29	—	·370	—
Total	66	394	6	2·148	2·8

TABLE 42

Males

Tuberculous Larynx.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	1	2	—	·007	—
23-27	1	9	—	·042	—
28-32	2	11	1	·064	15·6
33-37	2	11	—	·080	—
38-42	—	—	—	—	—
43-	—	—	—	—	—
Total	6	33	1	·193	5·2

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	8	28	3	·104	28·8
23-27	25	77	19	·331	57·4
28-32	27	100	17	·538	31·6
33-37	20	75	14	·518	27·0
38-42	14	42	8	·382	20·9
43-	15	46	10	·778	12·9
Total	109	368	71	2·651	26·8

Group 3.

Age Grade	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	5	12	4	·043	93·0
23-27	12	31	9	·133	67·7
28-32	16	24	13	·120	108·3
33-37	9	15	7	·096	72·9
38-42	10	21	9	·177	50·8
43-	20	36	15	·563	26·6
Total	72	139	57	1·132	50·4

TABLE 43

Females

Tuberculous Larynx.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	1	8	—	·026	—
23-27	1	6	—	·023	—
28-32	1	9	—	·045	—
33-37	—	—	—	—	—
38-42	—	—	—	—	—
43-	1	9	—	·128	—
Total	4	32	—	·222	—

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	6	17	4	·051	78·4
23-27	22	73	10	·264	37·9
28-32	14	55	9	·252	35·7
33-37	13	55	6	·324	18·5
38-42	9	28	6	·199	30·2
43-	11	27	6	·322	18·6
Total	75	255	41	1·412	29·0

Group 3.

Age Grade	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	3	5	3	·015	200·0
23-27	10	21	0	·074	81·1
28-32	12	27	8	·115	69·6
33-37	8	24	6	·140	42·9
38-42	3	13	1	·097	10·3
43-	17	54	10	·664	15·1
Total	53	144	34	1·105	30·8

TABLE 44

Males

Tuberculous Family History.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	15	72	3	·271	11·1
23-27	26	138	9	·609	14·8
28-32	29	150	7	·834	8·4
33-37	17	85	5	·607	8·2
38-42	8	42	1	·399	2·5
43-	8	41	1	·738	1·4
Total	103	528	26	3·458	7·5

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	21	105	9	·398	22·6
23-27	43	161	17	·693	24·5
28-32	32	114	18	·612	29·4
33-37	31	127	15	·902	16·6
38-42	25	108	7	1·008	6·9
43-	28	92	15	1·598	9·4
Total	180	707	81	5·211	15·5

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	7	15	5	·055	91·0
23-27	15	42	12	·179	67·0
28-32	13	36	9	·188	47·9
33-37	11	32	8	·224	35·7
38-42	14	31	9	·268	33·6
43-	8	21	8	·347	23·1
Total	68	177	51	1·261	40·4

TABLE 45

Females

Tuberculous Family History.

Group 1.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	9	50	1	·160	6·3
23-27	20	83	1	·306	3·3
28-32	22	121	3	·571	5·3
33-37	14	79	3	·473	6·3
38-42	9	45	2	·338	5·9
43-	7	42	—	·546	—
Total	81	420	10	2·394	4·2

Group 2.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	20	78	12	·246	48·8
23-27	36	156	14	·581	24·1
28-32	38	151	14	·689	20·3
33-37	27	128	9	·755	11·9
38-42	21	78	9	·575	15·7
43-	22	68	8	·825	9·7
Total	164	659	66	3·671	18·0

Group 3.

Age Group	Number of Patients Discharged	Exposed to Risk	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
-22	8	13	7	·039	179·5
23-27	18	51	12	·188	63·8
28-32	23	81	15	·374	40·1
33-37	8	26	5	·153	32·7
38-42	9	23	7	·165	42·4
43-	11	30	7	·369	19·0
Total	77	224	53	1·288	41·1

TABLE 46

English Life Table No. 8

Rate of Mortality.

Values of q_x: where q_x is the probability of a person aged x dying within one year

Age	Males	Females	Age	Males	Females
16	·00259	·00257	46	·01158	·00904
17	·00279	·00268	47	·01231	·00956
18	·00302	·00278	48	·01308	·01012
19	·00326	·00286	49	·01391	·01072
20	·00348	·00295	50	·01482	·01140
21	·00366	·00304	51	·01586	·01217
22	·00378	·00313	52	·01701	·01304
23	·00386	·00321	53	·01827	·01399
24	·00392	·00330	54	·01963	·01502
25	·00400	·00340	55	·02111	·01615
26	·00411	·00351	56	·02272	·01736
27	·00425	·00364	57	·02444	·01865
28	·00440	·00379	58	·02629	·02002
29	·00458	·00394	59	·02827	·02149
30	·00478	·00411	60	·03042	·02310
31	·00502	·00430	61	·03274	·02487
32	·00528	·00451	62	·03521	·02676
33	·00558	·00473	63	·03782	·02874
34	·00590	·00497	64	·04065	·03093
35	·00624	·00523	65	·04375	·03342
36	·00659	·00549	66	·04720	·03633
37	·00695	·00575	67	·05102	·03975
38	·00731	·00602	68	·05518	·04364
39	·00769	·00630	69	·05973	·04794
40	·00811	·00660	70	·06470	·05259
41	·00858	·00694	71	·07013	·05753
42	·00909	·00730	72	·07613	·06274
43	·00964	·00768	73	·08273	·06830
44	·01024	·00809	74	·08988	·07429
45	·01089	·00854	75	·09751	·08079

APPENDIX B

The Calculation of the 'Exposed to Risk'.

The 'exposed to risk' is the number of years of life contributed to the experience by patients from the day of discharge from the sanatorium until the date 'last heard of', the date of death, or until the close of observations. The observations closed on the anniversary of discharge in 1916.

The formation of the 'exposed to risk' is governed by the definition of the 'rate of mortality' which it is desired to ascertain. The 'rate of mortality' in respect of any year elapsed since discharge is the proportion of patients who enter upon that year, and who do not complete it owing to death having intervened. This involves the assumption that no patients are lost sight of during the year, and that a complete record of each of them is available. This condition, however, does not obtain here, and in actual practice it hardly ever does. With regard to the year 1916, the terminal year of observation, and also with regard to the recorded dates when some of the patients were 'lost sight of', it is not known whether the patients concerned actually completed the year of discharge in which they were living at those dates. In view of this,

it might be thought that a proper course would be to exclude such uncompleted years, but by so doing the 'exposed to risk' would be under-estimated. A better plan is to include them on the principle that an exposure for a fraction of a year is equivalent to a fractional exposure for a whole year. Thus, if in the year of exit twelve patients each contributed three months' exposure, this may well be considered equivalent to a full year's exposure in respect of three of them only.

These considerations will, to some extent, make clear the rationale of the procedure actually adopted.

Since the records of the after-histories of patients had been kept with such completeness, it was possible to construct the 'exposed to risk' by a method analogous to the 'policy year' method used in the construction of mortality rates from the experience of life assurance institutions. This method, when applied to the present data, consists in following each patient from the day of discharge until the same date in the following year, and so on to each anniversary of discharge until the patient passed out of observation.

It was assumed that the age given by a patient on admission to the sanatorium was half a year younger than the exact age; that is to say, if the age were given as 25, it would imply that this age was attained on the last birthday, which on the average would be six months ago. On this assumption, the exact age at admission would be $25\frac{1}{2}$. To this the period spent in the sanatorium was added, and the nearest age in the result was taken to represent the exact age at discharge. In the particular case of a patient who was admitted at age 25 last birthday, and who received five months' treatment, the nearest age at discharge would be 26.

The data were tabulated in what is known to actuaries as 'select' form, that is, in respect of each age grouping, according to the number of years elapsed since discharge and not according to the age attained. The total number of patients discharged in any particular age group was first ascertained, and then, by deducting the number of patients who passed out of observation from time to time, the number of patients who were observed to be exposed to the risk of dying in each of the nine years in the experience was calculated.

It was assumed that the nearest age, obtained as previously described, coincided with the date of discharge, and that each subsequent birthday synchronized with the successive anniversaries of discharge.

The work was much facilitated by recording on the experience card, in respect of each patient, the number of years of life contributed from the date of discharge until the date of passing out of observation. The manner in which the number of years of life or durations at exit were arrived at is immediately explained.

As already stated, only about 3·5 per cent. of the patients who left the sanatorium were 'lost sight of'. These patients were not necessarily lost sight of at an anniversary of discharge; in fact, many of them were last heard of at intermediate dates. In these cases the period of observation would include an odd number of months. It is obvious that no case could have been observed after the date 'last heard of', and yet it would not be correct to ignore fractions of a year contributed to the experience, since this would understate the numbers exposed to risk. A middle course was, therefore, adopted. Where the fraction of a year was less than six months, no account was taken of it, but where it exceeded that period it was treated as a whole year. On the average, this method of dealing with fractions of a year enables the facts to be represented fairly accurately. The durations for the cases 'lost sight of'

were, therefore, obtained by deducting the date of discharge from the date 'last heard of', and taking the nearest duration in the result. Therefore, if the period elapsed from date of discharge to the date 'last heard of' were 7 years and 9 months, the case would be tabulated as 'lost sight of' at nearest duration 8.

In regard to the patients who died, it should be noted that each of them must be observed up to the end of the year of discharge in which death occurred, since it is correct to assume that a patient dying in any particular year was exposed to the risk of death for the whole of the year. It is, therefore, not sufficient to take observation to the date of death only. Thus, a death occurring in the second year of discharge must be treated as 'exposed to risk' for the whole of the year between the first and second anniversaries. It should follow from this that the duration in the case of every patient who died would be calculated by taking the difference between the date of discharge and the date of death, with the provision that any odd months were to count as a whole year. In practice, however, the calculation of the durations in this way has been found, in the case of deaths, to be inconvenient as well as misleading. For instance, a death occurring three months after discharge from the sanatorium would receive a duration of 1 year; and it follows that no deaths would be tabulated at duration 0. If, now, it were necessary to calculate the rate of mortality at duration 0, the proper procedure would be to divide the deaths for that year by the corresponding 'exposed to risk'. But since the deaths in that year had been given a duration of 1 year, it would in every case be necessary to remember that the deaths to be used are those tabulated one year higher than the duration for which the rate of mortality was being calculated. In order to avoid this, it is the practice to arrange that the deaths shall be given a duration corresponding to the year in which they occur, and to tabulate them at a duration equivalent to the number of complete years elapsed since discharge. In following this plan, the odd months are automatically ignored, but, since in obtaining the 'exposed to risk' these odd months are, in each case, to be treated as a whole year, it is further arranged that the deaths shall not pass out from observation until the year following that indicated by the duration on the card. Thus, a patient who died within three months of discharge would be tabulated with a duration of 0 years and allowed to count in the 'exposed to risk' for the whole of that duration, but subsequently would be excluded by deduction in calculating the 'exposed to risk' for duration 1. This plan was, therefore, adopted.

The year in which the observations closed was, as already stated, 1916. It remains to calculate the durations of those patients who, as a result of the annual inquiries, were known to be living in that year. These cases are termed the 'existing' at the close of observations, and divide themselves into two categories:

(*a*) those who were known to be alive at the anniversary of discharge in 1916;

(*b*) those who were known to be living in 1916, but at a date prior to the anniversary of discharge.

In category (*a*) are included patients in respect of whom the information was received after the anniversary of discharge. These patients must have been alive at the date of the anniversary, and the exact time or duration of their exposure to risk of death is represented by the difference between the year of discharge and the year 1916. Category (*b*), however, includes patients in respect of whom the replies to the annual inquiries were forthcoming before the anniversary of discharge

in 1916. Thus, there is between the date of the reply and the anniversary a period in respect of which there is no information available. This special feature was met by tabulating each case with its nearest duration. For each patient the exact duration was obtained by deducting the date of discharge from the date 'last heard of' in 1916; from the result the nearest duration was readily calculated.

The durations having been inserted on the experience cards in accordance with the principles enunciated above, the next step was to sort the cards into the six age groupings, according to the age at discharge. The 'exposed to risk' was then calculated in respect of each age group for each duration. Taking age group 23–27, for example, the 'exposed to risk' in the first year since discharge or duration 0 was obtained for central age 25 by deducting the number of patients 'lost sight of' at duration 0 from the total number discharged at that age. This may be represented symbolically as under:

$$E_{(25)+0} = D_{(25)} - l_{(25)+0}.$$

The 'exposed to risk' in subsequent years was calculated from an application of the following formula, in which r is given successively the values 1, 2, 3, ...8.

$$E_{(25)+r} = E_{(25)+r-1} - d_{(25)+r-1} - l_{(25)+r} - e_{(25)+r}.$$

Where $D_{(25)}$ represents the number of patients *discharged* at central age 25.

Where $E_{(25)+r}$ represents the number of patients discharged at central age 25 who were '*exposed to risk*' of dying in the $(r+1)$th year.

Where $d_{(25)+r}$ represents the number of patients discharged at central age 25 who *died* during the currency of the $(r+1)$th year of discharge and who were tabulated as passing out of observation upon the $(r+1)$th anniversary of discharge.

Where $l_{(25)+r}$ represents the number of patients discharged at central age 25 who were tabulated as passing out of observation as '*lost sight of*' upon the rth anniversary of discharge.

Where $e_{(25)+r}$ represents the number of patients discharged at central age 25 who were *existing* at the close of observations in 1916 upon the rth anniversary of discharge.

An extract from the actual working schedules is exhibited in the following table:

Condition on Admission.

All Groups.

MALES

Age Group	Duration	Exposed to Risk	Lost Sight of	Existing	Actual Deaths	Expected Deaths	Ratio of Actual to Expected
	0	247	2	—	36	·988	
23–27	1	209	2	—	29	·859	
	2	153	2	25	22	·651	
	3	117	1	13	8	·515	
	4	96	1	12	9	·440	
No. of	5	71	—	16	5	·339	
Patients	6	54	1	11	3	·272	
Discharged	7	29	—	22	—	·153	
249	8	15	—	14	1	·084	
	9	—	—	14	—	—	
Total		991	9	127	113	4 301	26·3

The actual number of male patients discharged from the sanatorium in age group '23 to 27' inclusive is 249 : of these 9 were 'lost sight of', 127 were 'existing' at close of observations, and 113 died. The 'lost sight of', 'existing', and 'actual deaths' were separately sorted into groups according to the duration of exit as indicated on the card ; the number of cases in each group was counted and entered in the proper column on the correct line according to the mode of exit and years of duration respectively. The summation of the three columns gives. as it should, a total agreeing with the number of patients discharged, showing that each case has been accounted for.

The column headed 'exposed to risk' was next completed. The 'exposed to risk' at duration 0 was ascertained by deducting the numbers 'lost sight of' and 'existing' from the 'number of entrants', i.e. $249-2=247$. The 'exposed to risk' at duration 1 was similarly obtained from the number 'exposed' at duration 0 by deducting therefrom the 'lost sight of', the 'existing' at duration 1, and also the deaths at duration 0. These deaths were not deducted to obtain the 'exposed' at duration 0, since on the card the curtate duration or the number of complete years was tabulated. and, as previously pointed out, it is necessary to give to each case a full year's exposure in the year of death. Thus, the 'exposed to risk' at duration 1 is $247-2-0-36=209$. By continuing this procedure the 'exposed to risk' at the remaining durations were found. There is no tabulated exposure at duration 9 since of the 15 exposed at duration 8, 1 died and the other 14 passed out of observation at their anniversaries of discharge in 1916.

The calculation of the 'expected deaths' was made by multiplying the numbers 'exposed to risk' at the various durations by the appropriate 'rate of mortality', as shown by the standard table. Taking age group 23-27, for example, the 'expected deaths' for duration 0 were obtained by multiplying the 'exposed' at that duration by the 'rate of mortality' for the average age of the group, namely, 25 ; thus, $247\times\cdot004=\cdot988$. The 'expected deaths' for durations 1. 2. 3, &c., were obtained by the multiplication of the 'exposed to risk' at these durations by the 'rates of mortality' for ages 26, 27, 28, &c., respectively. The summation of these results gave the total number of 'expected deaths' for the group as 4·301 as against 113 who actually died. Thus, for each death expected, assuming the mortality rates of the general population to be operative, the comparison shows that 26·3 actually occurred.

The 'exposed to risk' and 'expected deaths' were calculated in the foregoing manner for each age group of the various medical classifications examined.

APPENDIX C

Note on

'An investigation into the effects of Family and Personal History upon the rates of mortality experienced in various classes of Life Assurance risks, with special reference to Tuberculosis.' By E. A. Rusher, F.I.A., and C. W. Kenchington, F.I.A., *Journal of the Institute of Actuaries*, Vol. xlvii, p. 433, 1913.

The data which formed the basis for this investigation were obtained from the records of a large number of impaired lives who proposed for life assurance to the Prudential Assurance Company, and who were accepted subject to diminishing debts of varying amounts being placed

upon the policies. In the event of death taking place during a prescribed period, the amount of the debt still outstanding would be deducted from the sum assured.

The investigation had special reference to 81,840 lives who, at the time of making the proposal, gave a family history of tuberculosis. All these lives were medically examined prior to the issue of the policy, and were considered favourable subjects for life assurance.

The data were in the first place divided into four main groups, according as the 'tuberculous history' appeared among (1) Lineals, (2) Lineals plus Collaterals, (3) Collaterals only, and (4) Distant Relatives only.

The method adopted to ascertain the excess mortality is that used in this report, viz.: to compare the 'actual deaths' with the 'expected deaths'. The latter were calculated by multiplying the 'exposed to risk' by the rates of mortality of the O[M] British Offices' Life Tables, 1893.

The experience of the males was throughout kept separate from that of the females, and further distinction was made as to the class of assurance effected, whether whole life or endowment assurance. The number who effected policies of the latter type constituted about 85 per cent. of the whole data.

The general results are given in Table A.

TABLE A

Family History of Tuberculosis.

Combined Experience of All Groups.

Percentage of Actual Deaths to those Expected according to O[M] Table.

First 10 Years of Assurance.

Type of Assurance	Age Group	Years of Assurance					
		0–4		5–9		0–9	
		Males	Females	Males	Females	Males	Females
Whole Life	–37	162	180	107	138	129	155
	38–52	132	122	102	99	114	108
	53–62	85	85	96	88	92	87
	Total	136	127	103	105	117	114
Endowment Assurance	–37	82	75	68	59	75	67
	38–52	66	54	61	49	63	51
	Total	77	67	66	55	71	61

The principal feature of this table is the difference between the mortality rates shown for the two classes of assurance. This variation in experience being so marked, it is thought that the type of life assuring in the two classes is fundamentally different. If the age distribution be taken into account, the percentages relating to the experience of the whole life cases would be increased and the differences in the mortality rates accentuated. In regard to this the authors express the opinion 'that the selection exercised by the assured is a most potent factor and practically of equal importance to the medical selection'. Another feature is the lighter rate of mortality experienced by female lives than by male lives. 'This feature is persistent for each group of entry ages and for each section of the Tables for the first 10 years of assurance, with the single exception of ages at entry below 38 under whole life assurances. The exception is noteworthy, as the excess mortality is considerable and coincides with the results of previous experiences under

whole life assurances on female lives. It may possibly point to the fact that under endowment assurances the spinsters are in greater proportion than the married women.' After making a further analysis of the results the authors go on to say ' that the effect of a definite family history of tuberculosis shows itself mainly in the younger ages at entry and the early years of assurance'.

As between a family history of lineals and collaterals, it is concluded that at least as much attention, if not more, must be given to a history of tuberculosis amongst brothers and sisters as amongst parents.

The general summary of this section of the investigation given by the authors is as follows :—

'Throughout the whole of the comparative Tables on male lives it will be noticed that the excess mortality is greatest in the youngest group of ages at entry, and that it is practically confined to the first 10 years of assurance. This feature is unmistakeable, and it is also shown in a marked degree in the Table for female lives. When each experience is compared with the normal mortality for the corresponding class of assurance, it will be seen that there is no trace of excess mortality in the endowment assurances above age 37 at entry, and in the whole life assurances after about age 50 at entry. Furthermore, the *degree* of tuberculous family history is of much less importance than the age at entry, and may, in fact, be said to have no practical value for assurance purposes over 35 at entry.'

An investigation was also made into the mortality of cases which not only had a family history of tuberculosis, but also presented personal blemishes. These blemishes were mainly indifferent health or poor physique, and included weights markedly below the standard.

TABLE B

Percentage of Actual Deaths to Expected Deaths.

Tuberculous Family History *plus* Personal Defect.

First 10 Years of Assurance. Males.

Type of Assurance	Age Group	Years of Assurance		
		0–4	5–9	0–9
Whole Life	–37	208	164	181
	38–52	103	191	157
	53–62	270	250	259
	Total	164	191	180
Endowment Assurance	–37	92	92	92
	38–52	108	103	105
	Total	97	96	96

A comparison of these results with those previously given in Table A indicates that the addition of a personal defect to a family history of tuberculosis involves a very considerable increase in the mortality rates.

The following Table C exhibits the mortality of lives who, while having various personal defects, did *not* give a family history of tuberculosis.

The data were divided into four sections according to the type of blemish observed.

(1) Not robust, poor physique, delicate or anaemic-looking, fair or indifferent health, physical appearance.

(2) Tuberculous glands, haemoptysis, tuberculous bone disease, lupus, incipient phthisis in the past, exposure to infection of tuberculosis.

(3) Chest malformation, pleurisy, pneumonia, empyema, spinal curvature, bronchitis, lungs unsatisfactory, chronic laryngitis.

(4) Dyspepsia, infantile paralysis, nervous disposition, varicose veins, hernia.

The data in each of these sections being comparatively small, the mortality experience was investigated only for male lives accepted for endowment assurance.

TABLE C

Percentage of Actual Deaths to Expected Deaths.

Personal Defects as in Sections 1, 2, 3, and 4.

First 10 Years of Assurance.

Endowment Assurance. Males.

Ages at Entry	Years of Assurance											
	0–4				5–9				0–9			
	1	2	3	4	1	2	3	4	1	2	3	4
–37	90	124	168	78	105	119	138	115	97	121	152	97
38–52	106	219	229	122	76	155	192	112	90	189	208	116
Total	94	146	189	94	97	127	159	114	95	137	172	104

These results, when compared with those given in Table A, are not without significance. 'The exposures are very few, but, as might have been expected, the Tables confirm the commonly expressed opinion that, where there is a personal history of tuberculosis or pulmonary disease, the rates of mortality are much higher than where there is a family history of these diseases. This is the case even where the latter is associated with indifferent health or poor physique.'

It would appear that for endowment assurances a very fair comparison may be made between Table B and section 1 of Table C. In both of these tables the personal defects are of a similar type, while the cases included in Table B present a family history of tuberculosis in addition. The data upon which these tables are based are not extensive, and, as would be expected, the results for each age group are not very consistent. However, taking the totals, irrespective of age, the results are almost identical. If this comparison be relied upon, it would appear that in the case of lives with a personal blemish of the nature indicated a family history of tuberculosis is of comparatively little account. This result may, in part, be due to the fact that in cases presenting a family history in addition to a personal history of tuberculosis, a more stringent selection was exercised by the assuring office.

The authors suggest, however, that deductions from the comparisons must be made with caution, since in all cases the acceptance of the assurance risk by the company was conditional on a surcharge in the nature of a contingent debt. 'This debt formed a heavy initial deduction from the sum assured rapidly diminishing with the duration of the policy. In the circumstances it is arguable that only lives who considered themselves to have a reasonable expectation of surviving the contingent debt period would take up a policy surcharged in this manner.'

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The Influence of Alcohol on Manual Work and Neuro-muscular Co-ordination

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Approved for publication by the Medical Research Committee, June 27, 1919.

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INTRODUCTION

The present report embodies the chief results of some work done at the instance of the Central Control Board (Liquor Traffic) by Dr. Vernon and his colleagues, whose studies were discussed and approved by the Scientific Advisory Committee to the Board. Dr. Vernon made this investigation while conducting on behalf of the Medical Research Committee some inquiries into industrial fatigue for the Health of Munition Workers Committee (Ministry of Munitions).

The main results obtained from these studies of the effects of alcohol on manual work and the co-ordination of fine muscular movements agree well with those reported by Dr. Mellanby (Report No. 31 of the present series), who made direct chemical estimations of the rates of appearance of alcohol in the blood after drinking, and of its disappearance from the blood under varied conditions. In particular, both these observers, using widely different methods, have shown the important differences between the effects produced by alcohol when taken with or without food respectively, and this is a question of practical interest which has been, as Dr. Vernon remarks, 'curiously ignored by most previous investigators'. The relations between the consumption of food and the physiological effects of absorbed alcohol are so important, as these recent studies have shown, that much previous work upon the effects of alcohol is now seen to have been impaired in value by disregard of the presence or absence of food in the stomach during the experiments.

Dr. Vernon's use of accuracy and speed in typewriting as tests for measuring the influence of alcohol lies open at first sight to the objection that alcohol affects both the amount and the quality of the work done, and that as these two variable factors may be influenced in opposite directions, it is difficult to assign its proper value to each. In the present experiments, however, it was found that the action of alcohol always, with one slight exception, reduced the speed of typing, and increase the number of mistakes; but in order to bring the two variables to terms of a single variable, Dr. Vernon has adopted, in the chief series of experiments, the novel method of restricting voluntarily the rate of work attempted. Finding that the speed of work could be made to vary within narrow limits, he endeavoured to obtain a simple numerical result by taking the number of mistakes made in typewriting as his guide and correcting to a constant typewriting speed, on the supposition that a mistake made may be regarded as the equivalent of a certain (carefully estimated) time unit. In thus restricting speed voluntarily, Dr. Vernon has of course introduced psychological factors of some complexity, which need investigation on their own account. The element of uncertainty due to their introduction would make some hesitate to accept the results expressed in Dr. Vernon's tables for the influence of alcohol, if this influence had been of small magnitude.

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But the effects shown are so pronounced as to leave no doubt that even the smaller doses of alcohol had a definitely harmful influence in his subjects under experiment. His observations of the effects of taking alcohol with food are especially instructive here, because any disturbing factors of the kind just indicated are common to the observations made with and without food respectively, and cannot, therefore, be held to account for the much greater effects of alcohol shown when this is taken on an empty stomach. Again, in many of the experiments both on Dr. Vernon himself and on other subjects, no attempt was made to control the speed of typewriting, and yet these experiments gave similar results to those in which it was controlled.

The Committee are indebted to the Central Control Board for placing this report at their disposal, and they would here acknowledge on Dr. Vernon's behalf the valuable aid which he received from Dr. Sullivan, Captain Greenwood, and Mr. Dreyer.

May 30, 1919.

Medical Research Committee,
15 Buckingham Street,
Strand, W.C. 2.

THE INFLUENCE OF ALCOHOL ON MANUAL WORK AND NEURO-MUSCULAR CO-ORDINATION.

By H. M. Vernon, M.D., with contributions from W. C. Sullivan, M.D., Capt. M. Greenwood, R.A.M.C., and N. B. Dreyer.

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I. The Effects of Pure Alcohol on the Accuracy and Speed of Typewriting.

It is of great practical importance for us to know as accurately as possible what effects upon manual work are produced by the consumption of moderate quantities of alcoholic liquids. Considerable quantities admittedly have very deleterious effects, but the question is whether the equivalent of one to two pints of beer, or of two to four ounces of whisky, appreciably influences the speed and skill of the average manual worker. Investigation of the problem on an adequate scale by direct methods upon the ordinary class of manual worker is so difficult as to be almost impracticable, for even if permission be obtained to carry out the experiment on a sufficient number of workers (e.g. 20 or more), it would be almost impossible to make sure that these workers regularly consumed the experimental dose of alcoholic or control liquid for the three or more weeks over which the experiment ought to last, to the exclusion of the alcoholic drinks to which many of them are

accustomed. Hence it was thought best to try and carry out the experiments upon manual workers of a different social class, who would be more easily controllable and less likely to resent inquiries into personal habits, viz. upon typists. In its physical attributes, typing is comparable to the semi-skilled work of many manual labourers, for a moderate degree of proficiency can be attained by any young person in a few days, and considerable skill in a few weeks. The movements of the hands are quicker than those needed for most kinds of manual work, but not for all. For instance, in the operation of 'mouth-reamering' of small-arm brass cartridge cases, the cases are slipped on and off a rotating spindle at the rate of about three or four a second. Typing has the great advantages that its speed and accuracy can readily be measured, and it has, in fact, been used to some extent by previous investigators for determining the action of drugs. Rivers[1] typed for an hour twice a day for twelve days, during six of which caffeine was taken, and found that the caffeine improved his speed of typing, but made no difference in the number of typing errors. In another series of experiments, lasting eight days, 20 or 40 c.c. of alcohol were taken on three of the days. The results were irregular, but the 40 c.c. of alcohol seemed to diminish the speed of typing. Frankfurther[2] studied the influence of alcohol, tea, and coffee on himself, and found that a dose of 20 c.c. to 40 c.c. of alcohol slightly decreased his speed and considerably increased his errors. Frankfurther typed a long memorized passage, and after practising for thirty-seven days, or until he had acquired a steady speed, he took the alcohol for five days, alternating with non-alcohol days. Rivers appears to have transcribed long passages in his typing, but a source of error is introduced in this way, as passages vary in their ease of transcription. Hence in the experiments to be described a method was adopted which was somewhat similar to that of Frankfurther, but it made the typing approximate much more closely in its character to the repetition work of which most semi-skilled manual labour consists. A short passage which took two minutes or less to type was memorized, and was typed invariably in all experiments. In my own case the passage chosen contained 376 letters or stops and 83 spaces, whilst the travelling typescript holder had to be moved back and jerked on (for a fresh line) seven times. In other words, it necessitated the making of 473 co-ordinated movements. In my fastest typing time, viz. 89·4 secs., this meant an average of 5·3 movements per sec., and in my average time, viz. about 110 secs., 4·3 per sec. As I generally needed to look at the key I wished to strike, it meant that 376 of these movements were co-ordinated movements of both eyes and hands. My own series of experiments lasted altogether $7\frac{1}{2}$ weeks, and during each day of this period I typed my passage as a rule 28 times, and occasionally 60 times, whilst I was careful to do no other kind of typing. The time required for the typing was taken at first by means of a watch with a large central seconds hand, but for the last month with a stop-watch.

I found, like Frankfurther, that alcohol decreased the speed and increased the errors of typing, but it is advantageous for most purposes to co-ordinate and group these two variables together, so as to obtain

[1] W. H. R. Rivers, *Influence of Alcohol on Fatigue*. London, 1908.
[2] Frankfurther, *Psychol. Arbeit.* 6, p. 419, 1912.

a single numerical result to express the alcohol effect. With this end in view, I carried out the majority of the typings in the following manner: I typed my passage seven times, the first time at a medium pace, but the 2nd, 4th, and 6th times either at a pace designed to result in my making, on an average, about one error in the passage, or at a quicker pace designed to result in about three errors. During the 3rd, 5th, and 7th typings I typed at the reverse speed. A concrete instance will make the method clear:—

	Slow typing.		*Fast typing.*	
	Time in Seconds.	*Mistakes.*	*Time in Seconds.*	*Mistakes.*
8.47 p.m.	(115·8)	(1)		
8.50			102·0	3
8.53	110·0	0		
8.56			98·6	1½
8.59	106·0	1		
9.2			98·7	3½
9.5	109·4	1		
Mean	108·5	0·67	99·8	2·67

2·00 mistakes = 8·7 seconds, or 1 mistake = 4·4 seconds.

Here it will be seen that when I was typing the passage at a 'slow' rate I made on an average 0·67 of a mistake, and when at a 'fast' rate, I made 2·67 mistakes. The fast rate was 8·7 secs. quicker than the slow rate, and as 2·00 more mistakes were made, 1·0 mistake would have a time equivalent of 4·4 seconds. The individual time equivalents of a mistake determined in this way varied a great deal, and occasionally more mistakes were made when typing slow than when typing fast, but the averages of the time equivalents observed in five successive weeks were 4·4, 4·6, 4·2, 4·5 and 5·0 seconds per mistake, or were nearly constant. Hence the average equivalent of 4·5 seconds per mistake was always adopted in all the corrections subsequently referred to. This plan of obtaining a time equivalence is a rough method which is approximately correct only under the particular conditions of experiment, and does not hold through a wide range of typing speed. For instance, if one tries to type beyond a certain speed one greatly increases the number of errors, but without achieving any increase of speed. Conversely, an inaccurate typist like myself makes occasional mistakes, however slowly he types.

It will be noted that the first typing in the above scheme is not averaged with the rest. The reason is that this typing is considerably slower (as a rule about 12 seconds) than the rest, and is more irregular, but its special features will be discussed later on. The 'half' mistakes recorded were due to a (correct) key being struck badly, and so making only a very faint typing impression.

Though the typings took less than two minutes each, as a rule, they were repeated only at three-minute intervals. As I began my experiments on this system I continued it for the five weeks for which the main experiment lasted, but it is not recommended as it is wasteful of time. A half-minute between successive typings would be quite sufficient. If alternate slow and fast typings are made, an interval of some sort is required in order to enable one to collect one's thoughts and realize fully the proposed speed of the next typing, but if the

typing is done throughout at a medium speed; as in some of the experiments to be described subsequently, it is best to make the successive typings as fast as possible one after the other.

The Main Experiment.

The main experiment lasted five weeks, during the first and fifth of which I was under normal conditions. In the second week I took 30 c.c. of pure alcohol (to which were added 10 c.c. of fruit syrup, and water to 150 c.c.) with my dinner at 7.0–7.30, and in the fourth week I took 60 c.c. of alcohol (diluted to 200 c.c.) with my dinner. In the third week I drank 30 c.c. of alcohol (diluted to 150 c.c.) at 5 p.m., on an empty stomach, for it was $3\frac{1}{4}$ to $3\frac{1}{2}$ hours since I had last had food, and I took none until 7.30 p.m., when the typing was finished. As a rule the typing was repeated four times a day, viz. 9.0 to 9.20 a.m., 6.30 to 6.50 p.m., 8.40 to 9.0 p.m., and at 10.30 to 10.50 p.m. The mean times of typing (excluding the first time the passage was typed) are quoted in Tables I to V at the end of the paper. These times were kept to very closely except on the few occasions specially mentioned in the foot-notes.

It will be seen that the times required for typing were fairly steady from day to day, but that the number of mistakes made was much more variable. On the right side of each Table are quoted the means of the typing times and the mistakes of both slow and fast typings, and it will be seen that the average number of mistakes is fairly steady, as it varied only from 1·9 to 2·7 in the first normal week, and from 1·7 to 2·7 in the final normal week. I practised the typing for four days previous to the experimental period, but the average typing times for successive weeks, viz. 122·1, 115·4, 109·6, 107·0, and 106·8 seconds, show that I acquired extra speed with practice, and did not reach an approximate level of speed until the last fortnight.

The averages for the various typing times are recorded at the bottom of the Tables, and they are reproduced again in Tables VI to VIII,

TABLE VI.—*Normal Weeks.*

Mean time at which typing was made.		Time taken.		Mistakes made.		Mean values.		Mistakes corrected to constant typing speed.
		Slow typing.	Fast typing.	Slow typing.	Fast typing.	Time.	Mistakes.	
First normal week (Feb. 8 to 13)	9.11 a.m.	127·1	118·2	1·7	2·8	122·7 } 122·0	2·2	2·4
	6.51 p.m.	124·7	118·1	1·0	3·0	121·4 }	2·0	1·9
	10.2 p.m.	126·0	118·4	1·4	3·8	122·2	2·6	2·6
Final normal week (Mar. 7 to 13)	9.10 a.m.	112·2	103·3	1·9	3·3	107·8 } 106·4	2·6	2·9
	6.42 p.m.	108 9	100·9	1·1	2·4	104·9 }	1·8	1·5
	8.58 p.m.	110·4	102·0	0·9	2·9	106·2	1·9	1·9
	10.42 p.m.	111·0	105·7	1·1	2·7	108·4	1·9	2·3

along with the means of the data obtained in the slow and fast typings. From Table VI we see that during both of the normal weeks the typing speed increased slightly between 9.10 a.m. and 6.47 p.m., whilst the number of mistakes diminished. The improvement of neuro-muscular co-ordination indicated by these data is well known in other kinds of manual work, and it occurs chiefly during the first few hours of the morning. It gradually becomes neutralized and eventually overpowered in the course of the day by fatigue effects. This influence of fatigue is shown in the present data, for the evening typings were slower and showed more mistakes than the 6.47 p.m. typings. In these and other experimental results subsequently recorded, it will be seen that the speed of typing varied comparatively little under all conditions, whilst the number of mistakes might vary fivefold. Hence, in order to obtain a single numerical result to show the effects of fatigue or of alcohol, the number of mistakes is taken as the standard, but this number *is corrected to a constant typing speed*, on the supposition that 4·5 seconds are equivalent to one mistake. In Table VI each normal week is regarded separately, and the mistakes are corrected to the mean typing speed of the 9.10 a.m. and 6.50 p.m. observations in the respective weeks, viz. to 122·0 and 106·4 seconds. Thus the speed at 9.10 a.m. during the last week being 1·4 seconds slower than the mean, and 1·4 seconds being equivalent to 0·3 mistake, the corrected number of mistakes becomes 2·9 instead of 2·6. The corrected mistakes recorded in the last column of the Table show that the diurnal variations of mistakes during the two normal weeks corresponded moderately well. The reason why the mistakes are not corrected to the mean speed of all four sets of daily observations is in order to obtain comparable data to those yielded in the alcohol experiments, when the 9.10 a.m. and 6.50 p.m. observations were the only ones made under *normal* conditions.

In Table VII are shown the effects of taking alcohol with food. The food was eaten between 7.0 and 7.30 p.m., the alcohol being drunk between about 7.5 and 7.25, or at an average time of appoximately 7·15. A typing was made 105 minutes after this time in the 30 c.c. alcohol experiment, and 96 minutes after in the 60 c.c. alcohol experiment. Subsequent experiments showed that these times were too late, as the maximum effect of 60 c.c. of alcohol was found to develop about 40 minutes after its consumption. They were chosen on the strength of Dodge and Benedict's[1] conclusions that the maximum depressive effect of alcohol upon various reflexes occurred at about 95 minutes after its administration. As the alcohol was taken by their subjects some time after any food had been consumed, I thought that the maximum effect of alcohol taken with food would be somewhat later than the time fixed by them.

The data in Table VII show that if the necessary allowance be made for fatigue, the 30 c.c. of alcohol had little if any effect on the speed of typing, but it increased the mistakes by 67 per cent., whereas the data obtained in the last normal week show that fatigue alone increased them only by 6 per cent. between the 6.42 and 9.0 p.m. typings. The influence of the alcohol was specially marked in the slow typings, for the mistakes were then increased 157 per cent. The

[1] Dodge and Benedict, *Psychological Effect of Alcohol*, Washington, 1915, p. 257.

corrected mistake values (corrected to the mean speed of typing observed in the 9.15 a.m. and 6.41 p.m. typings) show 100 per cent. increase at 9.0 p.m., as against a 27 per cent. increase at the corresponding time in the last control week. At 10.40 p.m. they show a 69 per cent. increase, as against a 53 per cent. increase in the control week; or, in other words, the effect of the alcohol had almost disappeared 205 minutes after it was consumed.

From the lower half of Table VII it will be seen that 60 c.c. of alcohol slightly increased the time of typing, whilst it nearly doubled the average number of mistakes. In the slow typings the mistakes were increased 140 per cent., whilst the corrected mistakes show an increase of 116 per cent. at 8.51 p.m. At 10.42 p.m. the increase was only 32 per cent., or considerably less than in the control experiment,

TABLE VII.—*The Effects of Alcohol taken with Food at 7.5 to 7.25 p.m.*

Mean time at which typing was made.		Time taken.		Mistakes made.		Mean values.		Mistakes corrected to constant typing speed.
		Slow typing.	Fast typing.	Slow typing.	Fast typing.	Time.	Mistakes.	
30 c.c. alcohol (Feb. 14 to 20)	9.15 a.m.	119·3	112·0	0·7	3·4	115·6 (114·6)	2·1	2·3
	6.41 p.m.	119·0	108·1	0·7	2·8	113·6 (114·6)	1·8	1·6
	9.0 p.m.	120·1	110·5	1·8	4·2	115·3	3·0	3·2
	10.40 p.m.	122·1	112·0	1·5	3·0	117·0	2·2	2·7
60 c.c. alcohol (Feb. 28 to Mar. 6)	9.10 a.m.	111·7	103·7	2·2	3·8	107·7 (106·6)	3·0	3·2
	6.38 p.m.	109·5	101·8	1·8	3·6	105·6 (106·6)	2·7	2·5
	8.51 p.m.	111·4	105·4	4·3	5·6	108·4	5·0	5·4
	10.42 p.m.	110·1	102·4	2·6	4·3	106·3	3·4	3·3

so not only had the depressant effect of the alcohol entirely passed off, but it appeared to have been followed by a stimulant effect. Still, the data are not adequate enough to permit a definite conclusion. In Fig. 1 the corrected mistake values for the normal weeks and for the alcohol weeks are reproduced diagrammatically. The particular form in which the alcohol curves are drawn depends on results which are discussed later on, but however drawn they show very clearly the onset and duration of the effects. The dotted lines indicate the average mistakes made in the normal weeks.

The mean results obtained in the third week, when 30 c.c. of alcohol (diluted to 150 c.c.) were taken at 5.0 p.m. on an empty stomach, are recorded in Table VIII. The effects were greater than those produced by 60 c.c. of alcohol with food, for 52 minutes after consuming the alcohol the mean typing time was increased 5·6 seconds, and the mistakes were increased 105 per cent. In the slow typings the mistakes

were increased nearly threefold, whilst the corrected mistakes show an increase of 162 per cent. This very marked effect was due partly to the fact that the typing was done at a time which subsequent experiments showed to be only about 22 minutes later than the optimum, for this occurs about 30 minutes after the alcohol is taken. The greater

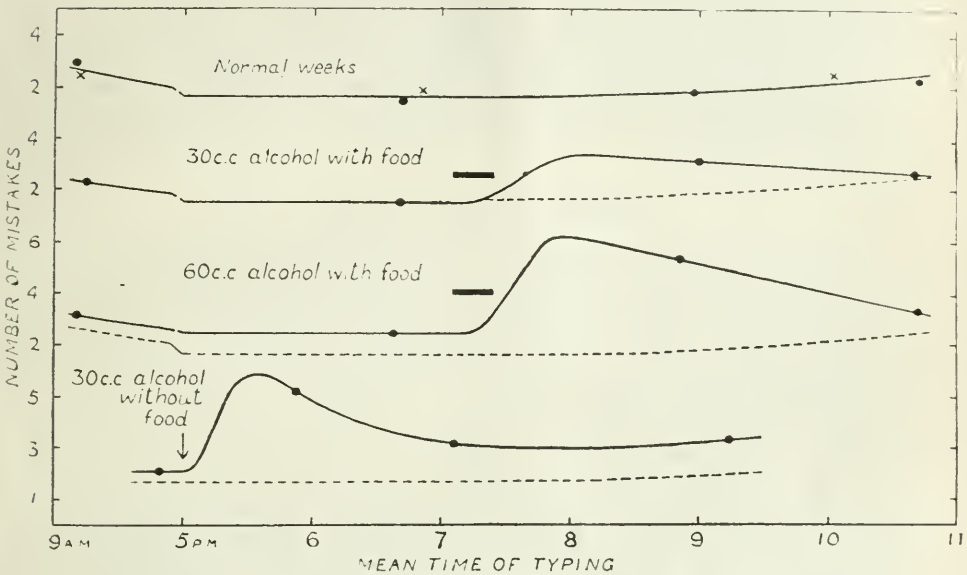

Fig 1.

Table VIII.—*The Effects of 30 c.c. Alcohol at 5 p.m. on an Empty Stomach.*

Mean time at which typing was made.	Time taken.		Mistakes made.		Mean values.		Mistakes corrected to constant typing speed.
	Slow typing.	Fast typing.	Slow typing.	Fast typing.	Time.	Mistakes.	
4.50 p.m.	110·2	102·2	1·1	3·0	106·2	2·1	2·1
5.52 ,,	115·5	108·1	3·1	5·5	111·8	4·3	5·5
7.6 ,,	114·0	104·7	1·4	3·5	109·3	2·5	3·2
9.14 ,,	115·8	106·0	1·3	3·3	110·9	2·3	3·3

effect was also due, in small degree, to the alcohol being in somewhat more concentrated form than in the alcohol + food experiments. Though the alcohol was taken in 20 per cent. solution in the one food experiment, and in 30 per cent. solution in the other, its admixture with the food in the stomach must have reduced its effective concentration to something between a third and a half these values,

whereas there was no dilution whatever of the 20 per cent. alcohol in the foodless experiment. Allowing for these two factors, this experiment, coupled with those subsequently described, shows that *at the height of its influence alcohol is about twice as active in upsetting neuro-muscular co-ordination when taken on an empty stomach as when taken with food.* The corrected mistakes observed in the foodless experiment are reproduced at the bottom of Fig. 1, and a comparison with the normal curve seems to indicate that recovery from the alcohol was not complete even at 9.14, or $4\frac{1}{4}$ hours after it was taken. This lack of complete recovery, whether genuine or not, was not observed in the other experiments which are described subsequently. In any case, one may say that most of the effect had disappeared two hours after the alcohol was taken.

Subjective Effects of Alcohol.

In my own case the subjective effects of alcohol are considerable, but I am probably more susceptible than the average man. I have always been practically an abstainer, and have been absolutely so for the last three years. The 30 c.c. of alcohol with food produced a slight degree of vertigo, but when taken without food it produced considerable vertigo, and a feeling of clumsiness at typing. My fingers appeared sometimes to strike the wrong key in spite of my best endeavours to strike the right one, and I frequently failed to hit the keys plumb in the middle. I felt rather stupid and sleepy, especially after taking 60 c.c. of alcohol with food, but otherwise felt neither mental exaltation nor depression. I found no difficulty in correcting my typing results even at the height of the alcohol effects, but my memory was poorer and more confused. For instance, in experiments to be described subsequently I typed four times successively without any pause at intervals of approximately two minutes, and I began each typing by putting the time, e.g. 6.0, 6.2, 6·4 and 6·6. When I was not under the influence of alcohol I could remember the appropriate time I had to insert without delay, but after alcohol I needed to pause to think, so I found it easier to get the time by looking at the (ordinary) watch which I kept by the side of the stop-watch. The maximum subjective effect undoubtedly came on earlier—probably ten minutes or so—than the effects on neuro-muscular co-ordination, and disappeared earlier than these effects disappeared, but it was not possible to obtain exact data on the point.

Alcohol Tolerance. The present series of experiments offer a good opportunity for determining whether I acquired any alcohol tolerance in the course of the three alcohol weeks. The method by which I investigated the question is best illustrated by giving an example in detail, and the one chosen relates to the week in which 30 c.c. of alcohol were taken without food. A mean was taken each day of the typing times and mistakes in the 4.50 p.m. observations, and the mistakes were corrected to the mean typing speed of the whole week, viz. 106·2 seconds. The same process was repeated for the 5.52 observations, the mistakes still being corrected to the mean typing speed (106·2 seconds) observed in the 4.50 observations. The corrected mistakes were now considerably more numerous than before, because

of the alcohol taken at 5.0 p.m., and Table IX shows the daily excess of these corrected mistakes. Though the excess was irregular, it was distinctly larger in the first half of the week than in the last half,

TABLE IX.—*The Effects of 30 c.c. Alcohol without Food at 5 p.m.*

Date.	Typing at 4.50 (before alcohol).			Typing at 5.52 (after alcohol).			Excess of corrected mistakes.
	Time taken.	Mistakes made.	Mistakes corrected to speed of 106·2 secs.	Time taken.	Mistakes made.	Mistakes corrected to speed of 106·2 secs.	
Feb. 21	109·2	2·1	2·8	113·5	5·2	6·8	4·0
,, 22	107·3	2·2	2·4	115·5	5·0	7·1	4·7
,, 23	103·7	2·2	1·6	111·2	5·4	6·5	4·9
,, 24	109·8	1·9	2·7	112·8	4·1	5·6	2·9
,, 25	104·0	2·3	1·8	108·0	2·5	2·9	1·1
,, 26	106·0	1·9	1·9	111·3	4·6	5·8	3·9
,, 27	103·6	1·9	1·3	110·2	3·3	4·2	2·9
Mean . .	106·2						3·5

i.e. the diminution in the excess seems to point to an increasing tolerance to the alcohol. However, on repeating this method of investigation with the 6.43 and 8.56 observations made during the two weeks in which alcohol was taken with food, no similar diminution of effect showed itself. In fact there was, if anything, a

TABLE X.—*Excess of Mistakes at 8.56 p.m. (or 5.52) as compared with those at 6.43 p.m. (or 4.50).*

Day of week.	30 c.c. alcohol with food.	60 c.c. alcohol with food.	30 c.c. alcohol without food.	Mean of alcohol experiments.	First normal week.	Final normal week.	Mean of normal weeks.
First	1·9	(1·2)	4·0	2·9	(0·8)	1·2	1·0
Second	1·9	2·0	4·7	2·9	0·0	0·2	0·1
Third	1·2	1·2	4·9	2·4	0·4	0·7	0·5
Fourth	1·8	4·3	2·9	3·0	0·7	0·6	0·1
Fifth	0·1	2·4	1·1	1·1	0·4	0·8	0·6
Sixth	1·7	2·1	3·9	2·6	1·7	1·2	1·4
Seventh	2·6	4·3	2·9	3·3	1·5	0·4	0·6
	1·6	2·7	3·5	2·6	0·8	0·4	0·6

diminution of tolerance in the 60 c.c. alcohol experiment, and the mean of all three sets of data, which is given in Table X, shows that on an average there was no definite change during the course of the week. This absence of tolerance is of significance in another respect, for it shows that my results were not in any way influenced by suggestion. Rivers found in his ergograph experiments that he sometimes achieved a better result on the days in which alcohol or other drug was taken than on control days, as he was more interested in the experiment, and so concentrated more energy upon it. In the typing method it is improbable that suggestion has any effect whatever on the result, for one has to keep one's attention fixed on the work in hand throughout, especially if one is not a skilled typist. One has not only to remember the memorized passage correctly, but one has (at least it was so in my own case) constantly to remind oneself of the intended speed of typing. I myself always tended to go too fast, and thereby to make an undue number of mistakes. The daily excess of corrected mistakes in the normal weeks, which is recorded on the right side of Table X, shows that on an average the 8.56 observations always contained more mistakes than the 6.43 observations, the mean daily excess being 0·6. If this value be subtracted from the mean values observed in the alcohol experiments, we find that the difference, which represents the pure alcohol effect, comes to 2·9 when 30 c.c. of alcohol were taken without food, 1·0 when 30 c.c. were taken with food, and 2·1 when 60 c.c. were taken with food.

Equivalence between Time and Mistakes. As already mentioned, the time equivalent of a mistake was estimated by dividing the mean difference of the number of mistakes made in the fast and slow typings into the mean difference of time taken. The equivalents determined in this way are recorded in Table XI. Though the

TABLE XI.—*Equivalents between Time and Mistakes.*

Approximate time of typing.	Normal week, Feb. 8 to 13.	30 c.c. alcohol with food, Feb. 14 to 20.	60 c.c. alcohol with food, Feb. 28 to Mar. 6.	Normal week, March 7 to 13.	Mean.	Time of typing.	30 c.c. alcohol without food, Feb. 21 to 28.
9.11 a.m.	8·1	2·7	4·9	6·4	5·5	4.50 p.m.	4·2
6.43 p.m.	3·3	5·2	4·2	6·2	4·7	5.52 p.m.	3·1
8.56 p.m.	3·2	6·7	4·5	3·3	4·4	9.14 p.m.	4·9
10.41 p.m.							
Mean . .	4·4	4·6	4·5	5·0	4·6		4·2

average for each week varies only from 4·2 to 5·0 seconds, or is nearly constant, there is much more variation between the individual values. During each of the normal weeks the time equivalents dwindled

rapidly in the course of the day, and a mean of the data for four weeks (the week in which alcohol was taken without food being excluded because of the different observation times) shows a fairly steady, though small, gradation. Though the data are not sufficient to warrant a definite conclusion, it seems probable that the time equivalence of a mistake does undergo definite variations in the course of the day, and tends to become smaller with the onset of fatigue. In other words, a fatigued person, when he quickens up his speed, tends to make mistakes more frequently than a fresh person does for a similar quickening.

Comparison of First and Subsequent Typings. As already mentioned, the first of the series of seven typings made each time was a good deal slower than the rest. The mean times of all the typings observed in the last normal week are shown in Table XII, and

TABLE XII.—*Means of Normal Week Typings.*

	Mean time taken.		Mean mistakes made.	Mistakes corrected to speed of 108·4 secs.	
1st typing	118·4		2·5	4.7	
2nd ,,	108·8		2·4	2·5	
3rd ,,	106·6		2·1	1·7	
4th ,,	106·5	108·4	2·3	1·9	1·7
5th ,,	106·2		1·8	1·3	
6th ,,	105·7		1·9	1·3	
7th ,,	106·9		1·9	1·6	

we see that the first typing was 10 seconds longer than the mean of the whole. Corrected to constant typing speed, the mistakes numbered 4·7, as compared with 1·7 in the subsequent six typings. By comparing the mistakes made in the first typing, after correction to constant speed, against the mean of the mistakes made in the subsequent six typings, it was found that in the normal weeks and the pre-alcohol observation periods of the alcohol weeks the excess of mistakes in the first typing was usually about 2 or 3, as can be seen from Table XIII. When 60 c.c. of alcohol were taken with food, however, the excess of mistakes increased to 5·6, and when 30 c.c. were taken without food, it increased to 6·6. In other words, when, an hour or so after the consumption of alcohol, I *first* began to execute co-ordinated muscular movements, I was relatively much more clumsy than I became after a minute or two's practice. The alcohol induced *an initial excess of clumsiness* which was considerably greater than the average excess of clumsiness indicated by the results recorded in previous pages. This conclusion, if established by subsequent observations, is one of great practical importance with reference to the causation of industrial accidents, for it means that a workman who started his work when under the influence of a certain quantity of alcohol would have at the outset a special liability to make

errors in his co-ordinated movements, i.e. he would be specially liable to meet with an accident, or to spoil his work.

TABLE XIII.—*Mean Excess of Mistakes in the First Typing over those in Subsequent Typings.*

Approximate time of typing.	First normal week.	Final normal week.	30 c.c. alcohol with food.	60 c.c. alcohol with food.	Time of typing.	30 c.c. alcohol without food.
9.11 a.m.	1·9	3·3	2·4	1·9	4.50 p.m.	2·8
6.43 p.m.	2·8	2·5	2·9	2·7	5.52 p.m.	6·6
8·56 p.m.	1·1	2·7	1·0	5·6	7·6 p.m.	2·9
10·41 p.m.		3·7	1·9	2·6	9.14 p.m.	3·5

In the observations in which 30 c.c. of alcohol were taken with food there was no indication whatever of this special clumsiness in the initial typing, and in the observations described in the next section, when typing was done at short intervals during the onset of the alcohol effects, there was likewise no indication of it. In other words, it looks as if the special clumsiness only develops if a fairly considerable dose of alcohol is taken, and the co-ordinated movements are altogether suspended for some time after.

The Influence of Dilution of the Alcohol.

In the above-described experiments the alcohol was taken in 20 per cent. solution when the dose was 30 c.c., and in 30 per cent. solution when it was 60 c.c. These concentrations correspond to the amount of alcohol present in spirits after dilution with about an equal volume of water, and it is usually admitted that when taken in such a form the alcohol is more potent than if an equal quantity be taken in a more dilute form, e.g. as beer. Hence it was of interest to investigate the effects of dilution of the alcohol by the typing method. For this purpose a different procedure was adopted from that employed in the main experiment. The memorized passage was typed four times successively without any delay between each typing, other than that required to note the time and re-set the stop-watch. Such processes took about 7 seconds, and as the average typing time was about 105 seconds, it meant that active co-ordinated movements were made for about $7\frac{1}{2}$ minutes altogether. This typing was repeated every twenty minutes, or there was a rest of $12\frac{1}{2}$ minutes between the typings. After making three fourfold typings under normal conditions to serve as a control, 30 c.c. of alcohol in the requisite dilution were drunk, and eight more typings were made. In this way the onset, culmination, and disappearance of the alcohol effects could readily be observed. The average number of mistakes made in each of the typings was corrected to the average speed observed in the three initial control observations. The typings were begun at 4 p.m., and the alcohol was drunk at 4.52 to 4.54, or $3\frac{1}{4}$ hours after food was last taken.

In that it would have been unpleasant to drink a large volume of cold liquid quickly, the alcohol was always diluted with warm water, and 10 c.c. of fruit syrup were added as usual. No food was taken until the typings were completed, viz. at 7.28 p.m.

In Tables XIV and XV are recorded the results obtained on two days when a volume of 30 c.c. of alcohol was drunk in 40 per cent. strength, and on two other days when it was drunk in 20 per cent. strength. A mean of the corrected mistakes in each pair of experiments is given, and also a mean of the two pairs of means. The alcohol was drunk in the course of about half a minute at 4.52 in

TABLE XIV.—*The Effects of 30 c.c. Alcohol in 40 per cent. Solution.*

Mean time of typing.	March 20.			March 23.			Mean corrected mistakes.
	Time taken.	Mistakes made.	Mistakes corrected to a speed of 103·1 secs.	Time taken.	Mistakes made.	Mistakes corrected to a speed of 103·0 secs.	
4.4 p.m.	106·5	2·0	2·8	106·2	2·8	3·5	3·1
4.24 „	102·1 (103·1)	2·5	2·3	99·8 (103·0)	1·9	1·2	1·8
4.44 „	100·7	3·6	3·1	102·9	2·4	2·4	2·7
4.52 „	alcohol	—	—	alcohol	—	—	—
5.4 „	102·7	5·5	5·4	101·8	6·4	6·1	5·7
5.24 „	106·9	5·9	6·7	101·5	6·0	5·7	6·2
5.44 „	106·7	6·6	7·4	102·7	4·9	4·8	6·1
6.4 „	102·3	5·5	5·3	101·5	3·9	3·6	4·5
6.24 „	100·5	4·4	3·8	101·1	2·6	2·2	3·0
6.44 „	99·5	3·8	3·0	100·0	2·8	2·1	2·6
7.4 „	101·5	4·2	3·8	99·4	3·6	2·8	3·3
7.24 „	101·5	3·5	3·1	100·0	3·6	2·9	3·0

the 40 per cent. dilution experiments, and when typing was begun at 5.0, or 8 minutes later, a very marked effect had already developed. It will be seen from the Table that at 5.4, i.e. the mean of the 5.0 to 5.8 typing, the mistakes were more than twice as numerous as they had been in the previous control period, whilst at 5.24 and 5.44 they were slightly more numerous still. Then they quickly declined, and by 6.24, or 92 minutes after the alcohol was drunk, they were practically normal again. These results are shown diagrammatically in the uppermost curve of Fig. 2. The dotted line curve reproduced at its base is the mean of two control experiments in which no alcohol was taken at all, and it shows a considerable diminution in the mistakes between the first and second typings, and a much slighter

improvement in subsequent typings. When compared with this control, it will be seen that the effects of the alcohol culminated at 5.24, or 32 minutes after its consumption, and there was never quite a complete recovery.

In the two experiments with 20 per cent. alcohol the alcohol was drunk at 4.54, not 4.52, and the effect produced at 5·4 was very much less than before. At 5.24, however, it was even greater than at the corresponding time in the 40 per cent. alcohol experiments, and, as can be seen by comparing the curves in Fig. 2, the effects, taken as a whole, appeared somewhat greater. Probably this result is mis-

TABLE XV.—*The Effects of 30 c.c. Alcohol in 20 per cent. Solution.*

Mean time of typing.	March 17.			March 21.			Mean corrected mistakes.	Mean corrected mistakes in 20% and 40% solution experiments.
	Time taken.	Mistakes made.	Mistakes corrected to speed of 104·7 secs.	Time taken.	Mistakes made.	Mistakes corrected to speed of 102·3 secs.		
4.4 p.m.	106·8	2·9	3·4	106·9	3·9	4·9	4·1	3·6
4.24 ,,	103·8	2·6	2·4	102·2	3·4	3·4	2·9	2·3
4.44 ,,	103·6	1·9	1·7	97·8	3·0	2·0	1·9	2·3
4.54 ,,	alcohol	—	—	alcohol	—	—	—	—
5.4 ,,	105·2	2·9	3·0	97·6	5·4	4·4	3·7	4·7
5.24 ,,	106·0	5·4	5·7	103·0	8·4	8·6	7·1	6·7
5.44 ,,	106·6	3·5	3·9	102·5	7·7	7·7	5·8	5·9
6.4 ,,	108·2	6·0	6·8	102·3	3·9	3·9	5·3	4·9
6.24 ,,	106·4	4·4	4·8	101·1	3·5	3·2	4·0	3·5
6.44 ,,	103·8	2·8	2·6	96·1	4·4	3·0	2·8	2·7
7·4 ,,	104·7	3·7	3·7	98·9	4·4	3·6	3·6	3·5
7·24 ,,	99·2	1·8	0·6	100·3	3·0	2·6	1·6	2·3

leading, and is due to the smallness of the number of experiments made, so it is best to combine all four experiments, and the third curve in Fig. 2 shows the average result of drinking 30 c.c. of alcohol in 20 to 40 per cent. concentration.

In Table XVI are shown the results obtained in three experiments in which the alcohol was taken in 5 per cent. solution (i. e. diluted to 600 c.c., instead of 75 or 150 c.c.). The alcohol was drunk between 4.53½ and 4.54½, and the typing at 5.4 showed scarcely any effect. At 5.24 there was a considerable effect, and a still greater one at 5.44; but if the curve in Fig. 2 be compared against the 20 per cent. plus 40 per cent. alcohol curve it will be seen that the effects, taken as

a whole, were distinctly smaller. They were about three-fourths as great, and the culmination of the effect was 20 minutes later than in the concentrated alcohol experiments. The subjective effects of the dilute alcohol were distinctly less, and came on much less rapidly than with the concentrated alcohol, but there was no definite difference in

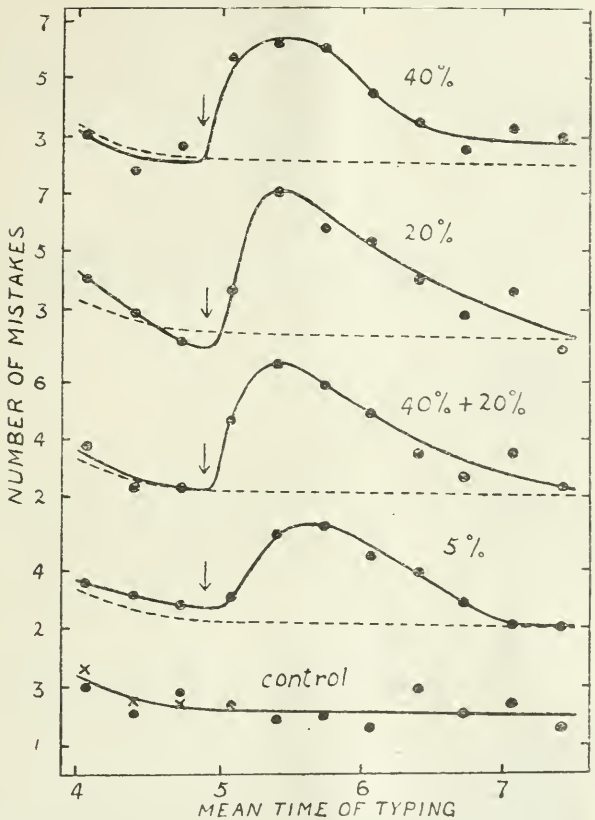

Fig. 2. The Effects of 30 c.c. Alcohol at Various Dilutions taken on an Empty Stomach.

the subjective effects of the alcohol when taken in 40 per cent. or in 20 per cent. concentration.

It may be concluded, therefore, that whilst alcohol taken on an empty stomach in concentrated solution does produce more effect than when taken in dilute solution, the difference is not very marked. No doubt beer is generally drunk off much more slowly than are spirits containing the same amount of alcohol, and this more protracted drinking of itself does much to diminish the alcohol effect of the beer.

TABLE XVI.—*The Effects of 30 c.c. Alcohol in 5 per cent. Solution.*

Mean time of typing.	March 19.			March 22.			March 25.			Mean corrected mistakes.
	Time taken.	Mistakes made.	Mistakes corrected to speed of 106·8 secs.	Time taken.	Mistakes made.	Mistakes corrected to speed of 102·6 secs.	Time taken.	Mistakes made.	Mistakes corrected to speed of 104·1 secs.	
4.4 p.m.	110·9	2·4	3·3	102·8	3·9	3·9	106·8	3·0	3·6	3·6
4.24 ,,	107·5 } 106·8	3·4	3·6	101·0 } 102·6	4·2	3·8	103·0 } 104·1	2·3	2·1	3·2
4.44 ,,	101·9	2·0	0·9	104·1	4·1	4·4	102·6	3·4	3·1	2·8
4.54 ,,	alcohol	—	—	alcohol	—	—	alcohol	—	—	—
5.4 ,,	104·8	2·1	1·7	99·4	3·4	2·7	105·3	4·7	5·0	3·1
5.24 ,,	102·8	4·6	3·7	102·3	5·5	5·4	106·6	5·9	6·5	5·2
5.44 ,,	102·4	5·9	4·9	104·7	5·6	6·1	108·0	4·6	5·5	5·5
6.4 ,,	102·7	3·9	3·0	100·8	6·4	6·0	104·6	4·3	4·4	4·5
6.24 ,,	102·8	3·7	2·8	101·7	4·8	4·6	104·9	4·2	4·4	3·9
6.44 ,,	104·1	2·4	1·8	102·2	4·1	4·0	102·7	3·0	2·7	2·8
7.4 ,,	102·0	2·5	1·4	99·2	2·6	1·8	104·4	3·2	3·3	2·2
7.24 ,,	102·5	1·5	0·5	104·9	3·2	3·7	98·5	2·9	1·7	2·0

The experiments recorded in Table XVII are the control experiments when no alcohol was taken. These results are reproduced in the bottom curve of Fig. 2. The crosses indicate the average numbers of mistakes made in the three control typings of the seven alcohol experiments.

TABLE XVII.—*Control Experiments.*

Mean time of typing.	March 24.			March 26.			Mean corrected mistakes.
	Time taken.	Mistakes made.	Mistakes corrected to speed of 104·6 secs.	Time taken.	Mistakes made.	Mistakes corrected to speed of 105·1 secs.	
4.4 p.m.	105·8	3·4	3·7	104·8	2·3	2·2	3·0
4.24 „	101·5 104·6	1·8	1·1	105·3 105·1	3·1	3·1	2·1
4.44 „	106·4	2·9	3·3	105·3	2·3	2·3	2·8
5.4 „	104·0	2·1	2·0	104·8	2·9	2·8	2·4
5.24 „	102·1	1·9	1·3	105·0	2·4	2·4	1·9
5.44 „	103·2	2·1	1·8	105·9	2·0	2·2	2·0
6.4 „	99·0	3·1	1·9	104·3	1·5	1·3	1·6
6.24 „	101·8	3·4	2·8	104·5	3·1	3·0	2·9
6.44 „	96·2	2·6	0·7	104·4	3·6	3·4	2·1
7.4 „	98·8	3·2	1·9	100·3	4·0	2·9	2·4
7.24 „	100·6	3·1	2·2	102·4	1·6	1·0	1·6

The Influence of the Quality of the Food on Alcohol Effects.

In the previously described experiments in which alcohol was taken with food, the diet was similar to that eaten under ordinary conditions, though it was mostly vegetarian and poor in fats. Care was taken not to drink any of the alcohol until a fair amount of food had been eaten, so as to prevent the conditions of absorption resembling those obtaining in the experiments on an empty stomach. It was thought to be of interest to make a few experiments in which the diet differed substantially, so the effects of fatty and fatless food were tried. Two experiments were made with each kind of diet. The fatty food eaten consisted of sardines and oil, meat, cheese, butter, and other food calculated to contain about 55 grams of fat, whilst the fatless food consisted of beans, tomatoes, bread, rice, and jam, or food calculated to contain not more than 4 grams of fat. Three or four fourfold typings of the character above described were made at 20-minute intervals before the meal, which was taken at 7.0 to 7.30. The alcohol taken with it (60 c.c. diluted to 200 c.c.) was drunk at an

average time of about 7.16. Immediately after the meal the typings were begun again, and were continued at 20-minute intervals for the next $3\frac{1}{4}$ to $3\frac{1}{2}$ hours. The mistakes were corrected to constant typing speed as before, and the results obtained are recorded in Tables XVIII and XIX. The times of typing in each pair of experiments differed by 3 minutes, but this is practically a negligible difference, so means

TABLE XVIII.—*The Effects of 60 c.c. Alcohol with Fatless Food.*

	March 15.			March 18.			
Mean time of typing.	Time taken.	Mistakes made.	Mistakes corrected to speed of 106·4 secs.	Time taken.	Mistakes made.	Mistakes corrected to speed of 104·6 secs.	Mean corrected mistakes.
6.6 p.m.	106·2	3·0	3·0	106·9	1·0	1·5	2·3
6.25 „	107·6 (106·4)	2·4	2·7	105·6 (104·6)	1·8	2·0	2·3
6 47 „	105·4	1·6	1·4	101·4	2·4	1·7	1·6
7.5 to 7.25	alcohol	—	—	alcohol	—	—	—
7.37 p.m.	108·8	3·9	4·4	108·2	6·2	7·0	5·7 (6·1)
7.57 „	108·2	4·9	5·3	107·3	7·1	7·7	6·5
8.17 „	109·3	5·7	6·3	107·0	5·8	6·3	6·3 (6·4)
8.37 „	109·2	5·0	5·6	107·3	7·0	7·6	6·6
8.57 „	106·8	4·9	5·0	106·1	5·5	5·8	5·4 (4·9)
9.17 „	105·7	3·5	3·3	107·3	4·6	5·2	4·3
9.37 „	106·7	4·9	5·0	105·4	5·0	5·2	5·1 (4·6)
9.57 „	107·1	2·9	3·1	105·7	5·1	5·3	4·2
10.17 „	106·3	4·6	4·6	104·7	3·3	3·3	4·0 (3·8)
10.37 „	107·6	3·9	4·2	108·1	2·0	2·8	3·5
10.57 „	—	—	—	102·5	3·1	2·6	2·6

have been taken between the results of the two experiments in each case, and these means have been grouped so as to give the most even result. These results are shown diagrammatically in Fig. 3, and it will be seen that the maximum effect of the alcohol in each case developed very soon after the meal was completed, and then gradually diminished till in the fat-free experiment it reached, or nearly reached, normal level three hours later. In the fatty meal the initial effect produced by the alcohol was rather smaller, but it did not wear off nearly so rapidly, and even $3\frac{3}{4}$ hours after the meal there was still a considerable alcohol effect.

These experiments are not sufficiently numerous to base any very safe conclusions upon, but they strongly suggest that the more fat

TABLE XIX.—*The Effects of 60 c.c. Alcohol with Fatty Food.*

Mean time of typing.	March 14. Time taken	March 14. Mistakes made.	March 14. Mistakes corrected to speed of 110·1 secs.	March 16. Time taken.	March 16. Mistakes made.	March 16. Mistakes corrected to speed of 107·9 secs.	Mean corrected mistakes.
5.42 p.m.	104·7	2·6	1·4	113·3	2·5	3·3	2·4
6.2 „	— (110·1)	—	—	103·8 (107·9)	1·3	0·4	0·4 } 2·1
6.22 „	113·1 (110·1)	3·5	4·2	107·5 (107·9)	3·4	3·3	3·8 } 2·1
6.42 „	112·6 (110·1)	1·8	2·4	107·0 (107·9)	2·1	1·9	2·2
7 5 to 7.25	alcohol	—	—	alcohol	—	—	—
7.30 p.m.	112·3	3·6	4·1	120·5	7·7	10·5	7·3
7.50 „	111·4	4·6	4·9	111·8	7·4	8·3	6·6 } 6·1
8.10 „	106·1	2·8	1·9	109·3	6·4	6·7	4·3 } 6·1
8.30 „	112·1	5·3	5·7	107·6	6·0	5·9	5·8
8.50 „	108·2	5·5	5·1	107·6	5·4	5·3	5·2 } 5·5
9.10 „	108·6	5·4	5·1	109·3	6·1	6·4	5·7
9.30 „	109·4	5·1	4·9	106·7	5·5	5·2	5·1 } 5·4
9.50 „	114·6	6·1	7·1	106·6	5·4	5·1	6·1
10 10 „	111·1	3·0	3·2	107·7	4·6	4·6	3·9 } 5·0
10.30 „	115·5	3·2	4·4	114·0	6·6	8·0	6·2
10.50 „	105·6	2·5	1·5	105·5	5·4	4·9	3·2 } 4·7

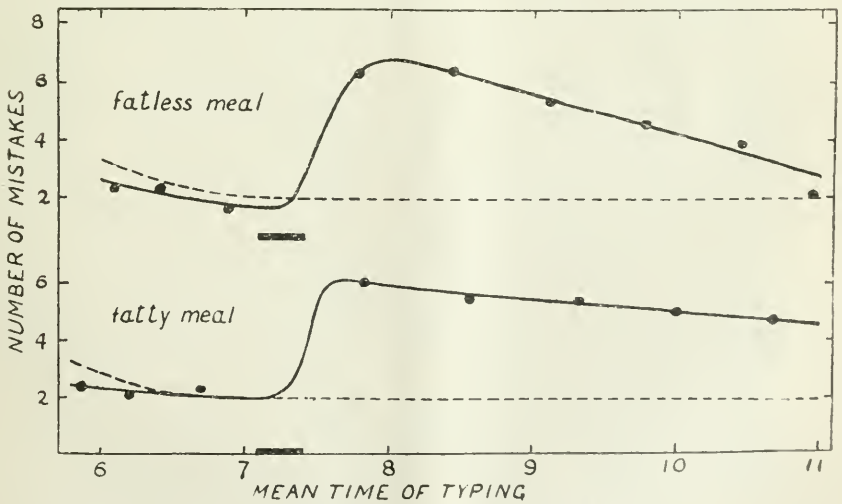

FIG. 3. The Effects of 60 c.c. Alcohol taken with Food.

present in the food the slower the absorption and metabolism of the alcohol taken at the same time. Fatty food is well known to be digested more slowly than fatless food, and a delay in the digestion of the meal as a whole would inevitably delay the complete absorption of the alcohol taken with it. But the fat acts also in another way. It has a considerable solvent power for the alcohol, so a portion of the alcohol cannot be absorbed until the whole of the fat is absorbed likewise.

The Influence of the Quantity of Alcohol taken.

The main experiment showed that when 60 c.c. of alcohol were taken with food, the effect produced was about twice as great as when 30 c.c. were taken. In order to determine more exactly the relative effects of the quantity of alcohol, a few experiments were made by the method of typing at 20-minute intervals, before and after drinking alcohol on an empty stomach. In two experiments, 20 c.c. of alcohol were taken about 3 hrs. 10 min. after food, and in one experiment 40 c.c. were taken. In each case the alcohol was diluted to the same volume, viz. 150 c.c., as in one of the previously described series of experiments with 30 c.c. of alcohol, or the concentration of the alcohol in the various experiments was 13·3, 20, and 26·7 per cent. respectively. It was thought that, in comparing the effects of quantity of alcohol, the conditions would be more comparable if the total volume of liquid were kept constant and the concentration variable, rather than concentration constant and volume variable.

TABLE XX.—*The Effects of 20 c.c. and 40 c.c. Alcohol without Food.*

Mean time of typing.	20 c.c. alcohol in 13·3 % solution.			40 c.c. alcohol in 26·7 % solution.		
	Corrected mistakes (1).	Corrected mistakes (2).	Mean.	Time taken.	Mistakes made.	Mistakes corrected to speed of 107·6 secs.
4.4 p.m.	2·0	1·0	1·5	109·2	1·4	1·8
4.24 ,,	0·0	2·0	1·0	108·5 (107·6)	2·5	2·7 (1·6)
4.44 ,,	0·5	1·2	0·8	105·0	1·1	0·5
4.54 ,,	—	—	alcohol	alcohol	—	—
5.4 ,,	1·2	0·1	0·6	105·2	2·6	2·1
5.24 ,,	1·7	1·2	1·4 (1·1)	110·9	4·0	4·7
5.44 ,,	1·1	0·5	0·8	119·8	5·3	8·0
6.4 ,,	1·0	0·1	0·6 (0·9)	113·0	3·0	4·2 (6·2)
6.24 ,,	2·1	0·4	1·2	112·9	7·0	8·2
6.44 ,,	1·7	0·7	1·2 (0·6)	109·3	2·9	3·3 (4·0)
7.4 ,,	0·0	0·0	0·0	110·2	4·1	4·7
7.24 ,,	0·3	—	0·3	106·1	3·2	2·9

The results of the experiments are recorded in Table XX, and they are reproduced graphically in Fig. 4. It will be seen that the 20 c.c. of alcohol were almost without effect, whilst the 40 c.c. had considerably more effect than 30 c.c., and distinctly reduced the speed of typing, as well as its accuracy. However, the effect is not as great as one would expect. The probable explanation is that these experiments with 20 and 40 c.c. of alcohol were made about nine months after those with 30 c.c. of alcohol, and only a fortnight after other experiments in which 45 to 60 c.c. of alcohol were taken on an empty stomach. These larger doses of alcohol probably reduced my susceptibility to alcohol to some extent. In any case, one may conclude that whilst 30 c.c. of alcohol greatly reduced the accuracy of my typewriting, two-thirds this quantity had a very small effect indeed. Experiments on other subjects, to be described later on, point to a similar conclusion, and show that, so far as typewriting is concerned, alcohol below a certain very moderate amount is practically without influence.

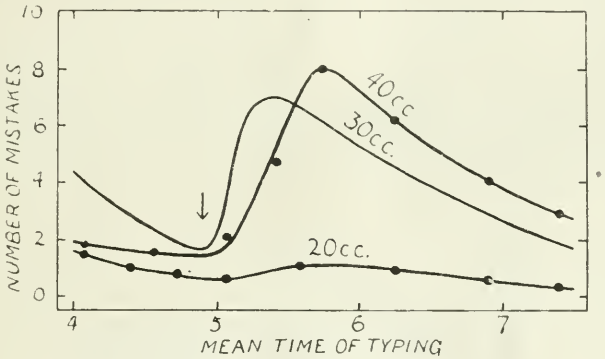

Fig. 4. The Effects of various quantities of Alcohol.

Further experiments upon the influence of alcohol on typewriting were made, at my suggestion, by Mr. N. B. Dreyer, of Trinity College, Oxford. Mr. Dreyer had no previous experience of typing, but after a fortnight's practice he was able to type sufficiently fast to get reliable results. He continued to make experiments on the influence of alcohol and alcoholic liquids on most days during the next two months. At first his average time for typing a memorized passage was 71 secs., but after ten days it fell to 62 secs., and in the next seven weeks it fell only to 56 secs., or he quickened up rather less than I did in the course of my five weeks' experiment. Mr. Dreyer followed nearly the same experimental procedure as myself. He typed the passage six times altogether, at slow and fast rates alternately, and from the data so obtained he calculated the numerical equivalent of a mistake, and thereby corrected his results to a constant typing speed. His 'time equivalent of a mistake' averaged 15 secs., or was more than three times as long as my own. Mr. Dreyer is practically an abstainer, and his susceptibility to alcohol diminished somewhat during the course of his experiments. Hence the experiments of any series were considered comparable only if they were made within a few days of one another.

Upon the effects of quantity of alcohol eight experiments were made. In all of them the alcohol was taken in the afternoon, three or more hours after food. Experiments were made with 20, 25, and 30 c.c. of alcohol in 20 per cent. strength, and another series with 30 c.c. of

TABLE XXI.—*The Effects of 20 to 30 c.c. of Alcohol without Food on N. B. D.*

Dates of Experiments.	Quantity of alcohol taken.	Concentration.	Number of mistakes made.			
			Before alcohol.	½ hr. after alcohol.	1 hr. after alcohol.	2 hrs. after alcohol.
May 11 and 17	20 c.c	20 %	1·1	1·7	1·1	0·9
May 12	25 c.c.	20 %	1·3	2·8	1·4	—
Apr. 30, May 5 and 13	30 c.c.	20 %	2·1	4·2	—	1·8
May 7 and 8	30 c.c.	14 %	2·2	4·5	—	2·4

alcohol in 14 per cent. strength. The numbers of (corrected) mistakes made are quoted in Table XXI, means having been taken when two or more experiments were made under the same conditions. From these values, and from the curves in Fig. 5, it will be seen that the

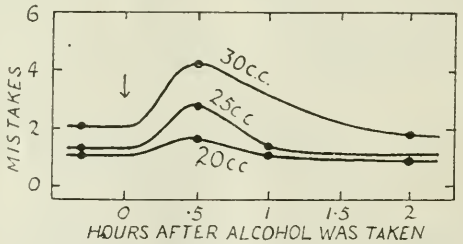

FIG. 5. The Effects of various quantities of Alcohol on N. B. D.

effect of the alcohol was more or less proportional to the quantity consumed. It is impossible to make an accurate comparison, as the number of mistakes made in the control typings, before the alcohol was drunk, was nearly twice as great in the 30 c.c. alcohol experiments as in the others.

In a group of four experiments, in which 40 c.c. of alcohol were taken at 7.0 to 7.30 with food, the effects produced were the following:

Date of Experiment.	Number of mistakes.		
	Shortly before food.	40 min. aft food.	3 hours after food.
Apr. 21	1·9	5·0	1·3
„ 22	1·6	2·2	1·7
„ 23	1·8	3·7	2·8
„ 24	1·9	4·3	1·7
Mean	1·8	3·8	1·9

These effects are about the same as those produced by taking 30 c.c. of alcohol on an empty stomach, and in the light of these and other experiments described subsequently, it appeared that Mr. Dreyer did not respond so differently to alcohol with and without food as most subjects do. In them, as in myself, alcohol is about twice as effective when taken on an empty stomach as when taken with food.

It is well known that individuals vary greatly in their susceptibility to alcohol, and this fact is well brought out by one of the three series of experiments made by a lady, K. D. V. She, like myself, is practically an abstainer, and has been completely so for the last three years. She typed the same passage as myself, and upon the same machine. She typed it five times on each occasion, with about half

TABLE XXII.—*The Effects of 22·3 c.c. Alcohol with Food on K. D. V.*

Normal week.					Alcohol with Food at 7 to 7.30 p.m.				
Date.	At 11.29 a.m.		At 8.54 p.m.		Date.	At 11.26 a.m.		At 8.37 p.m.	
	Typing time.	Mistakes.	Typing time.	Mistakes.		Typing time.	Mistakes.	Typing time.	Mistakes.
Feb. 26	119·6	2·2	136·8	4·0	Mar. 5	113·6	4·2	125·4	5·8
,, 27	124·4	4·3	—	—	,, 6	114·2	2·8	117·2	6·0
,, 28	125·4	3·2	132·0	3·6	,, 7	110·4	4·1	124·8	4·9
Mar. 1	119·6	2·2	131·4	3·9	,, 8	117·0	3·0	122·2	4·2
,, 2	115·4	4·8	129·8	3·0	,, 9	114·6	3·3	123·2	2·6
,, 3	118·4	3·4	125·8	1·6	,, 10	105·4	2·4	123·5	4·9
,, 4	122·0	3·6	130·2	5·1					
Mean..	120·7	3·4	131·0	3·5		112·5	3·3	122·7	4·7

a minute's rest between the typings. After practising occasionally for five days, she typed for a week under normal conditions at about 11.30 in the morning, and again in the evening at about 9.0 p.m. She then showed a considerable fatigue effect, as her average typing time was 10·3 seconds longer than in the morning, though the number of mistakes made was almost the same. During the next week she took 22·3 c.c. of alcohol (diluted to 150 c.c.) each evening with her dinner between 7.0 and 7.30, or at an average time of about 7.13. This quantity of alcohol was equivalent to the 30 c.c. drunk by myself, as our body weights were 55·3 and 74·4 kgm. respectively. A typing was made at or about 8.37, or 84 minutes after the time at which most of the alcohol was drunk, and from the data in Table XXII it will be seen that the mean typing time was 10·2 seconds slower than at 11.26 a.m., whilst 1·5 more mistakes were made. That is to say, the alcohol caused almost the same increment of mistakes as 30 c.c. of it had done in myself under very similar conditions. However,

K. D. V. said that her subjective sensations of vertigo—which were considerable—had been at a maximum immediately after the meal was over, and had largely disappeared when she did the typing, and there can be no doubt that a great deal of the lack of neuro-muscular co-ordination had disappeared likewise.

In the third week a typing was made at about 11.30 a.m., and immediately after it half the previous quantity of alcohol, or 11·2 c.c. (diluted to 100 c.c.), was drunk. This was upon an empty stomach, as no food had been taken for $3\frac{1}{4}$ hours. The typing was repeated at an average time of 20 minutes after the alcohol consumption, i.e. it was begun 14 minutes after, and finished 26 minutes after. As can be seen from Table XXIII, the effects were considerable, the number

TABLE XXIII.—*The Effects of 11·2 c.c. Alcohol without Food at 11.40 a.m. on K. D. V.*

Date.	At 11.34 a.m.		At 12 noon.		At 12.45 p.m.	
	Typing time.	Mistakes.	Typing time.	Mistakes.	Typing time.	Mistakes.
Mar. 13	115·8	2·8	118·6	5·9	—	—
,, 14	114·8	2·2	115·4	4·7	112·4	2·1
,, 15	111·2	1·6	113·8	3·2	110·2	2·9
,, 16	113·4	1·7	113·4	2·8	113·2	1·1
,, 17	113·4	3·8	117·0	5·3	113·8	1·9
,, 18	111·2	2·6	115·8	5·4	111·2	2·0
Mean . .	113·3	2·4	115·7	4·5	112·2	2·0

of mistakes being nearly doubled, and the typing time increased 2·5 seconds. A third typing was made at an average time of 65 minutes after the alcohol ingestion, and by then the effects had completely disappeared. In fact, the typing time was 1·1 secs. shorter than in the control experiments, and the mistakes were 0·4 fewer.

It will be realized that K. D. V. was extraordinarily susceptible to the action of alcohol when taken on an empty stomach. The effects appeared to develop more quickly in her than they did in myself, and they certainly passed off more rapidly, though in all probability this was merely the result of the smaller dose taken.

II. The Effect of Pure Alcohol on Neuro-muscular Co-ordination, as shown by the Target Method.

A large number of experiments have been made upon the effect of alcohol on various muscular acts, and many of them have been recorded and discussed at some length by the Advisory Committee.[1]

[1] Cf. *Alcohol: its Action on the Human Organism.* London, 1918.

The experiments fall into three main classes, for they were made on (1) reflex movements, such as the knee-jerk and eye-closing reflex; (2) simple and unskilled movements, such as the speed with which a finger can be moved to and fro, the strength of the finger muscles in raising a load (tested by ergograph), and the speed with which the eyes can be turned towards a fresh object; (3) complex muscular acts, such as hill-climbing and the manipulation of recording apparatus. The Committee concluded that though moderate doses of alcohol (40 c.c. or less) had very little effect on the performance of simple muscular acts requiring no skill, they distinctly impaired the performance of skilled acts. However, the skilled muscular acts investigated were not well defined, nor was the effect of alcohol upon them measured quantitatively, so I thought it to be of interest to make some further observations. The method employed was a very simple one, which I have designated the 'target' method.

The Target Method. Upon squared paper, preferably ruled in millimetres, rows of ten ink dots are made at distances of two centimetres or more apart. The paper is pinned on to a nearly vertical drawing-board, and at such a level that the uppermost spots are approximately at shoulder height. The subject of experiment stands squarely facing the board, at such a distance that he can just reach and prick the paper with the sharp pointed instrument (e.g. a small awl) held in his hand, when he stretches out to arm's length. He has a few preliminary trials to get his correct distance, and this, once ascertained, should be fixed by drawing a chalk mark on the floor, against which he 'toes the line'. Then the subject puts his hand against his chest, and when he has steadied himself, he extends his hand at a moderate speed and tries to prick the uppermost spot on the left-hand side of the paper. He withdraws his hand quickly until it touches his chest, and then extends it again, and pricks the next spot below. He continues this process at a steady rate, pricking each of the ten spots in succession, and then he starts working upwards on the next row of ten spots, till he finally arrives at the level at which he started. This pricking of the 20 spots usually takes 50 to 60 seconds, and the time required was found to remain very steady throughout a series of experiments, even when no mechanical method was adopted to make it constant. After the first few experiments, however, I followed Dr. MacDougall's suggestion of pricking the paper synchronously with the ticks of a metronome, which gave 20 double ticks in 55 seconds. As a precaution against error, the time of each experiment was always taken by means of a stop-watch, held in the left hand of the subject.

The distance of each prick from its spot was subsequently measured to the nearest millimetre, and a mean of the 20 distances taken. As a rule the distance was about 2 mm., and it could be read off at a glance. The sheets of paper used had space enough for twelve rows of ten spots each, or were sufficient for six experiments. The pricking experiments were usually repeated at three-minute intervals, and after eight of them had been made, to serve as a normal, the dose of alcohol was taken, and the experiments were continued for an hour at three-minute intervals. Then, for the next hour or less, they were made at six-minute intervals. The chief objection to the method, when

employed on absolutely fresh subjects, lies in the considerable improvement of accuracy in pricking the target which is shown in the course of successive experiments. For instance, four medical students showed an average error of 2·53 mm. in their first experiment, but this dwindled down to 1·70 mm. in their last experiment made 101 minutes later. However, we shall see that it is possible to make an allowance for this improvement. In my own case, doubtless because of considerable practice, there was no improvement of accuracy after the first four experiments, or latterly, after the first two experiments.

TABLE XXIV.—*The Influence of 30 to 60 c.c. Alcohol on Target-pricking Errors.*

Times of experiments.	Volume of alcohol taken at 11.31 a.m.				
	30 c.c.	37·5 c.c.	45 c.c.	52·5 c.c.	60 c.c.
11.8 and 11.11	—	1·63	1·80	2·05	1·87
11.14 and 11.17	—	1·85	1·60	1·70	1·35
11.20 and 11.23	2·09	1·58	1·80	1·82	1·77
11.26 and 11.29	1·93	1·57 1·67	1·52 1·59	1·73 1·77	1·53 1·62
11.31	— 1·94	—	—	—	—
11.34 and 11.37	1·95	1·67	1·43	1·82	1·82
11.40 and 11.43	1·99	2·08	2·47	2·63	1·98
11.46 and 11.49	2·15	2·60	2·75	3·10	2·70
11.52 and 11.55	2·16	2·45	2·75	3·72	3·05
11.58 and 12.1	2·17	2·32 2·39	3·20	3·50 3·41	4·50
12.4 and 12.7	2·25 2·17	2·50	3·25 2·92	3·28	3·90 3·76
12.10 and 12.13	2·10	2·10	2·65	3·45	3·55
12.16 and 12.19	2·16	2·25	2·75	3·00	3·78
12.22 and 12.25	2·15	2·03	2·33	2·87	2·92
12.28 and 12.31	1·98	1·95	2·57	2·55	2·55
12.37 and 12.43	2·01	1·97	2·50	2·08	2·48
12.49 and 12.55	1·98	1·85	2·18	2·40	1·95
1.1 and 1.7	1·94	1·92	2·00	1·90	2·20
1.13 and 1.19	1·89	1·80	1·80	1·92	1·82
1.25 and 1.31	1·83	1·60	1·82	1·70	1·70
Increased error due to alcohol	12 %	43 %	84 %	93 %	132 %

The effects of various quantities of alcohol upon the accuracy with which the target was pricked are recorded in Table XXIV, and are reproduced in Fig. 6. The alcohol was taken at about 11.30 a.m., or rather more than three hours after food was last consumed. It was diluted with slightly warmed water to 300 c.c., or the concentration varied from 10 per cent. in the 30 c.c. experiments to 20 per cent. in the 60 c.c. experiment, except in three of the six experiments with 30 c.c. alcohol. These six experiments were made at different times of the year from the rest (viz. in May, June, and November), and will be referred to again later. The single experiments with larger doses were made at intervals of two or three days in December. In order to get more even results, the mean target-pricking errors of each consecutive pair of experiments have been averaged, but even then the irregularities are somewhat considerable. Hence, in plotting

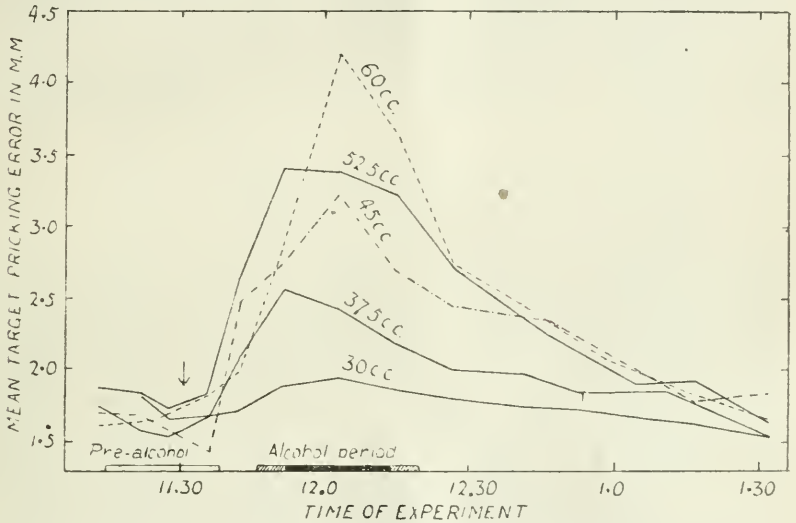

Fig. 6. The Effects of various quantities of Alcohol on Target-pricking Errors.

out these data in Fig. 6, some more of the consecutive results have been averaged. To get a normal, against which the alcohol effect could be compared, the errors observed in the three double experiments immediately before the alcohol, and in the one double experiment after it (i.e. before the alcohol began to exert its influence), have been averaged. Against this normal have been compared the average errors observed in the five consecutive experiments in which the alcohol produced the greatest lack of co-ordination. The incidence and duration of these normal and alcoholic periods are shown at the bottom of Fig. 6. It will be seen that even in the half-hour for which the alcohol effect was averaged there was no constancy, but a gradual waxing to a maximum, followed by a gradual waning. However, a more reliable result is obtained by averaging the alcohol effects over a half-hour period than over a shorter interval such as ten minutes.

From Table XXIV it will be seen that whilst the consumption of 30 c.c. of alcohol increased the target-pricking error only by

12 per cent., 37·5 c.c. increased it 43 per cent., or more than three times as much. With equal increments of 7·5 c.c. to the quantity of alcohol consumed, the error increased at the same rapid rate, for it will be seen from Fig. 7 that the relationship between the quantity of alcohol and the error induced is practically a linear one. No experiments were made with smaller doses of alcohol than 30 c.c., but if the straight line joining the experimental values be produced, it cuts the abscissa at 27 c.c., or indicates that such a dose would have induced no extra lack of co-ordination whatever. In the light of the previously recorded experiments on typewriting, we may conclude that the curve is not strictly linear when it approaches the abscissa, but is curved in somewhat the manner indicated by the dotted line. In any case, smaller quantities of alcohol than 30 c.c. would have produced so slight a diminution of co-ordination as scarcely to be measurable. We may say, therefore, that above

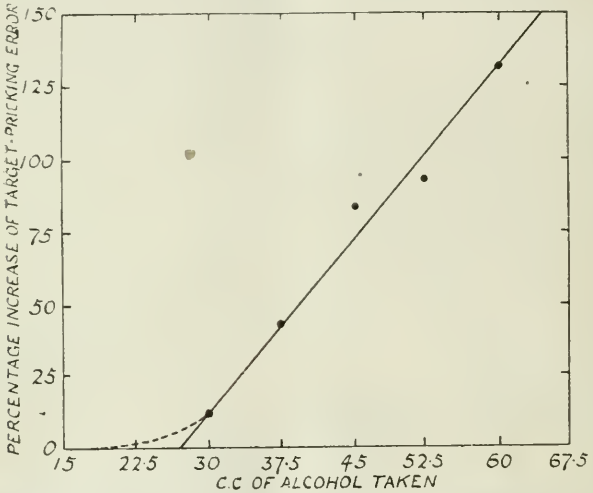

Fig. 7. Relationship between Target-pricking Error and quantity of Alcohol taken.

a certain minimum, *the adverse influence of alcohol on neuro-muscular co-ordination varies in arithmetical progression with the quantity taken.* This conclusion is confirmed by observations made by a totally different method. Sherrington and Sowton[1] showed that if a beating cat's heart were perfused with warm oxygenated salt solution containing a constant amount of chloroform, the height of the beat rapidly sank, but after a minute or two it attained an equilibrium level, and continued to beat unchanged for as long as twenty minutes. I made similar experiments with tortoise hearts,[2] which were perfused with cold oxygenated salt solution containing 1 to 4 per cent. of ethyl alcohol. As an average of eight experiments, I found that whilst 1 per cent. of alcohol depressed the level of the heart-beat 13 per cent., 2 per cent. depressed it 40 per cent., and 4 per cent. depressed it 83 per cent. These three values are almost exactly in linear proportion to the

[1] Sherrington and Sowton, *Thompson Yates and Johnston Laboratories Reports*, vol. v Pt. 1, 1903.

[2] Vernon, *Journ. Physiol.* vol. **41**, p. 194, 1910.

concentration, or the height of the heart-beat varied directly with the concentration of the alcohol. Experiments with eight other alcohols gave a similar linear relationship between height of beat and concentration of alcohol.[1]

The maximum dose of 60 c.c. of alcohol, taken on an empty stomach, produced considerable subjective effects. I felt extremely dizzy and sleepy, and, about 1½ hrs. after taking the dose, vomited slightly. I could still carry out the necessary manipulations of the experiment without much difficulty, and could walk quite straight along a chalk line marked on the floor, though this required a little effort. Still, a larger dose than that taken would probably have induced overpowering somnolence and inability to conduct the experiment.

It should be mentioned that, in order to make the mean result obtained in the 30 c.c. alcohol experiments conform to the experiments with 37·5 to 60 c.c. alcohol, which were carried out months later, the base line of normality on which it has been drawn in Fig. 6 has been arbitrarily lowered to the average normal level attained in these latter experiments.

III. The Effects of Wines and Spirits.

Comparison with the Effects of Pure Alcohol.

It is generally assumed that the influence of alcoholic liquids depends almost entirely upon the ethyl alcohol contained in them. If this assumption were valid, it would follow that the toxic action of pure alcohol, wines, spirits, and beer, if diluted to equal alcoholic strength, would be practically the same. As we have no exact proof of the validity of the assumption, it was thought to be of interest to make comparisons between the effects of alcohol and of various alcoholic liquids by means of the typewriting and neuro-muscular co-ordination tests.

Comparative experiments were made by Mr. Dreyer upon himself by the typing method. In one series, 35 c.c. of alcohol, diluted to

Table XXV.—*The Effects of 35 c.c. Alcohol with Food on N. B. D.*

Dates of experiments.	Alcoholic liquid taken.	Concentration.	Typing mistakes made			
			Shortly before alcohol.	40 mins. after.	1 hr. after.	2 hrs. after.
May 30	pure alcohol	10·2 %	0·6	1·9	1·5	0·8
June 4 and 5	whisky	10·2	0·4	1·2	1·4	0·5
May 29 and June 3	claret	10·2	0·6	1·3	1·0	0·7
May 23	pure alcohol	20	0·4	2·4	2·0	1·1
May 22 and 26	whisky	20	0·9	2·4	1·7	0·8

[1] Vernon, *Journ. Physiol.* vol. 43, p. 325, 1911.

10·2 per cent. strength, were taken with food (at 7.0 to 7.30 p.m.) in the form of whisky, claret, and as pure alcohol. From Table XXV it will be seen that two experiments were made with whisky and with claret, and one with alcohol. The mistakes made in these experiments have been corrected for variable speed of typing, and averaged, and

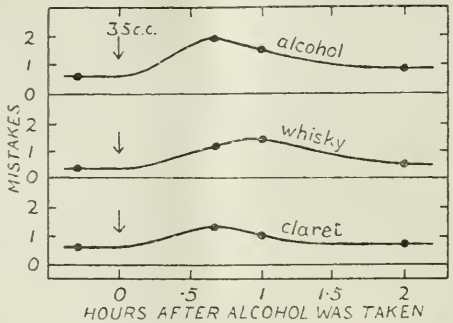

Fig. 8. The Effects of various Alcoholic Liquids on N.B.D.

the average results are shown in Fig. 8. It will be seen that the pure alcohol produced a slightly greater effect than the whisky, whilst the claret produced a slightly less effect. Another series of experiments was made about nine days earlier, with the alcohol in 20 per cent. concentration instead of 10·2 per cent. These results are not strictly comparable with the series just mentioned, as the subject showed some diminution of susceptibility throughout his experimental period. However, they are comparable amongst themselves, as are the previous series, as they were made at about the same time. They likewise show that 35 c.c. of pure alcohol, taken with food, had rather more influence than 35 c.c. in the form of whisky.

Another series of experiments was made a fortnight after the first of the two series just mentioned. Four experiments were made with 20 c.c. of alcohol, or its equivalent in the form of claret and whisky, and four with 30 c.c. of alcohol, or its equivalent in claret. In every

Table XXVI.—*The Effects of 20 and 30 c.c. Alcohol, without Food, on N. B. D.*

Dates of experiments.	Alcoholic liquid taken.	Typing mistakes made			
		Shortly before alcohol.	½ hr. after.	1 hr. after.	2 hrs. after.
June 12 and 16	pure alcohol (20 c.c.)	0·3	0·9	0·5	0·2
June 19	whisky ,,	0·2	0·6	0·1	0·1
June 17	claret ,,	0·2	0·6	0·2	0·3
June 11 and 13	pure alcohol (30 c.c.)	0·4	1·1	0·4	0·3
June 14 and 15	claret ,,	0·3	1·3	0·5	0·3

experiment the alcohol was taken in 10·2 per cent. solution at about 4.30 p.m., or three hours after food. From Table XXVI it will be seen that 20 c.c. of pure alcohol produced rather more effect than its equivalent as whisky and claret, whilst on the other hand 30 c.c. of alcohol produced rather less effect than its equivalent as claret. On an average, therefore, the alcohol and claret had about the same effect.

On comparing these foodless experiments with the preceding series of food experiments, it will be seen that 30 c.c. of alcohol on an empty stomach produced, if anything, less effect than 35 c.c. on a full stomach. Such a small influence of food is contrary to the results obtained with all the other subjects of experiment, and one must attribute the apparent contradiction, at least in part, to Mr. Dreyer's diminishing susceptibility.

The smaller response of Mr. Dreyer to claret and whisky than to pure alcohol is unexpected, and does not agree with the neuro-muscular co-ordination tests to be described. Doubtless different individuals vary in their response, and one may conclude that in any case the difference between pure alcohol and alcoholic liquids of equal alcoholic strength is a small one.

The neuro-muscular co-ordination tests upon myself were made by the target method in three groups of six experiments each. In each group I tested the effects of 30 c.c. of alcohol, taken (1) as pure alcohol in 10·2 per cent. and 40 per cent. strength,

TABLE XXVII.—*Effects of 30 c.c. Alcohol on Target-pricking Errors.*

Times of experiments.	Control experiments.	10·2 % alcohol.	40 % alcohol.	10·2 % brandy.	37 % brandy.	10·2 % claret.	Means of alcohol experiments.
4.49 and 52	1·85	2·17	2·00	2·00	2·05	2·05	2·05
4.55 and 58	1·87	1·98	1·88	1·68	1·73	1·73	1·80
5·0	no alcohol	alcohol	alcohol	alcohol	alcohol	alcohol	—
5.3 and 6	1·73	2·00	1·90	1·75	1·75	1·60	1·80
5.9 and 12	1·73	2·15	1·83	1·97	1·85	1·70	1·90
5.15, 18, 21 and 24	1·80	2·28	2·03	2·00	2·20	1·95	2·09
5.27, 30, 33 and 36	1·79	2·33	2·08	1·89	2·00	2·04	2·07
5.39, 42, 45 and 48	1·81	2·30	1·96	1·96	2·06	2·11	2·08
5.51, 54, 57 and 6.0	1·74	2·22	1·91	1·91	1·93	2·01	2·00
6.6 and 12	1·70	2·15	1·87	1·63	1·95	1·95	1·91
6.18 and 24	1·87	2·27	1·70	1·70	1·73	1·83	1·85
6.30 and 36	1·75	2·10	1·78	1·68	1·75	1·95	1·85
6.42 and 48	1·75	2·00	1·77	1·68	1·77	1·73	1·79
6.54 and 7.0	1·68	2·05	1·60	1·77	1·68	1·85	1·79

(2) as brandy, taken in 10·2 per cent. and 37 per cent. strength, (3) as claret, taken in 10·2 per cent. strength. Also a control experiment was included. The experiments of each group were made on consecutive days, the order in which they were made being changed in the different groups so as to eliminate any possible influence of diminishing susceptibility. In the series of

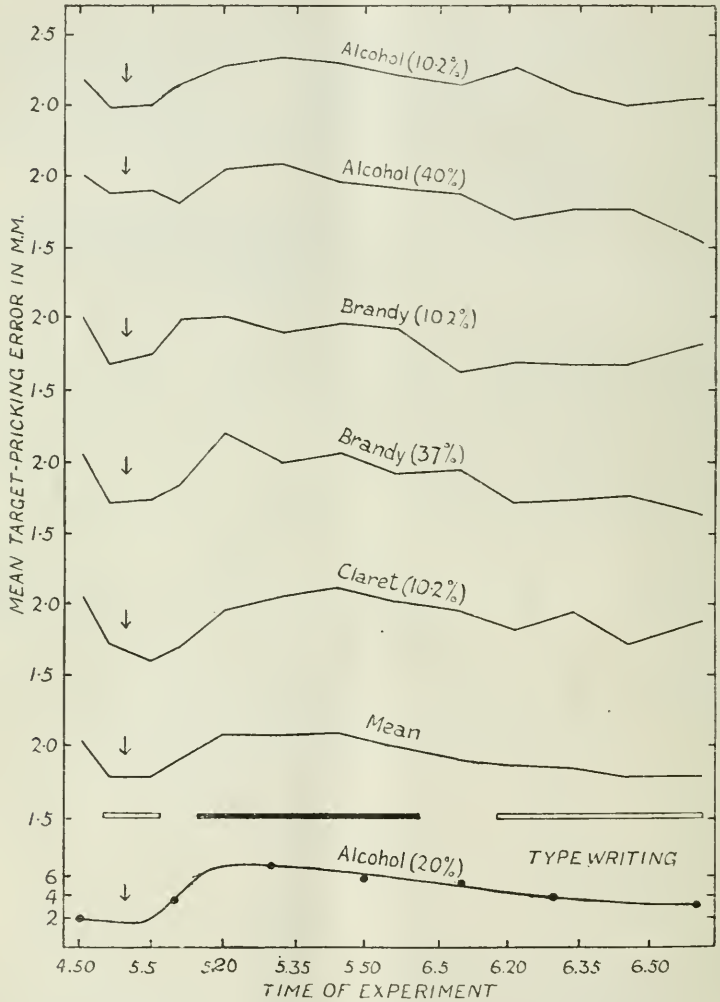

FIG. 9. The Effects of various Alcoholic Liquids on Target-pricking Errors.

experiments made in May and June, the alcohol was drunk at about 5.0 p.m., or about 3 hours 15 minutes after food was last taken. In the November experiments it was drunk at about 11.30 a.m., or 3 hours 5 minutes after food, but this slightly shorter interval made no appreciable difference in the result. The records given in Table XXVII show, not the individual results, but the means of each set of three experiments, with a further averaging of these

means in groups of two or four. That is to say, each value quoted represents the mean of 120 or 240 attempts to prick the target. These grouped values are reproduced in Fig. 9, where it will be seen that they yield fairly regular curves. Only four experiments at three-minute intervals were made before drinking the alcohol, and the first two of these must be ignored because of the increased error due to lack of practice. However, the effects of the alcohol did not appreciably develop for the first six minutes after it was drunk, so one can take the mean of the two experiments immediately before drinking the alcohol, and the two immediately after, as an index of the target-pricking errors made in absence of alcohol. It will be seen that the errors increased to a maximum about 20 to 40 minutes after the alcohol, and then gradually dwindled to the pre-alcohol average, which they practically attained within two hours. At the bottom of the figure is given the mean of all the fifteen alcohol experiments, and also, on a corresponding scale, the mean of the two typewriting experiments in which 30 c.c. of alcohol were taken in 20 per cent. strength (cf. Table XV). It will be seen that the general contour of the two curves is similar, for in each of them the maximum alcohol effect was attained after about 30 minutes, and had nearly disappeared after 2 hours.

In order to obtain a satisfactory numerical measure of the effect produced on neuro-muscular co-ordination by the various alcoholic liquids, it was thought best to compare the mean errors observed in the 46 minutes (between 5.15 and 6.1) when the alcohol effect was greatest with the mean errors observed in the 12 minutes (between 4.55 and 5.7) before the effect came on, and the 43 minutes (between 6.18 and 7.1) when it had largely disappeared. These periods of comparison are shown under the mean curve in Fig. 9. The numerical effects are recorded in Table XXVIII, and we see that, on an average, the dilute

TABLE XXVIII.—*Mean Target-pricking Errors observed when taking Various Alcoholic Liquids.*

30 c.c. alcohol taken in the form of	Mean error for 12 min. before and 43 min. after alcohol.			Mean error for 46 min. at height of alcohol effect.			% increase of error due to alcohol.			
	May.	June.	Nov.	May.	June.	Nov.	May.	June.	Nov.	Mean.
10·2 % alcohol	1·89	2·25	2·06	2·17	2·38	2·28	15	6	11	11
40 % „	1·62	1·78	1·91	1·83	2·10	2·05	13	18	7	13
Brandy containing 10·2 % alcohol	1·69	1·72	1·72	1·96	1·97	1·89	16	15	10	14
Brandy containing 37 % alcohol	1·70	1·97	1·54	2·05	2·26	1·82	21	15	18	18
Claret containing 10·2 % alcohol	1·65	2·15	1·53	2·02	2·29	1·81	22	7	18	16
Mean	1·71	1·97	1·75	2·01	2·20	1·97	17	12	13	14

alcohol caused 11 per cent. increase of target-pricking error, whilst the 40 per cent. alcohol caused a 13 per cent. error. The brandy was distinctly more effective, especially when taken neat, as in this form it caused an 18 per cent. error. Claret came midway between dilute and neat brandy, as it caused a 16 per cent. error. The mean error induced by alcoholic liquors was 16 per cent., as compared with 12 per cent. for pure alcohol of similar concentration. Hence there can be no doubt that in my own case brandy and claret were distinctly more toxic than pure alcohol.

The mean values obtained in the three control experiments are recorded in Table XXVII, and it will be seen that the target-pricking error remained nearly constant throughout the 132 minutes for which the experiments lasted. It was not possible to use these control values as a normal base line in the various alcohol experiments, for 'normality' varies appreciably from day to day. For instance, it happened that on the days when 10·2 per cent. alcohol was taken the average target-pricking error was considerably higher than usual.

The other subjects of experiment were five in number, viz. Messrs. T. H. Cathrall, N. B. Dreyer, M. H. MacKeith, D. B. Pauw, and another. They were all medical students, aged 21 to 24, and all but the anonymous student were, and always had been, of very temperate habits, though they were not abstainers. I wish to express my thanks to them for the care and enthusiasm with which they carried out the somewhat tedious experiments. The method of experiment was similar to that employed by myself, except that they did eight experiments at three-minute intervals before taking the alcohol, and twenty-six experiments after it, likewise at three-minute intervals, so in their case the whole experiment lasted 102 minutes. Four of the subjects of experiment took, on one occasion, 30 c.c. of alcohol diluted to 10·2 per cent. strength, and on another occasion 294 c.c. of claret, which likewise contained 30 c.c. of alcohol in 10·2 per cent. strength. The alcohol

TABLE XXIX.—*The Influence of 30 c.c. Alcohol on the Target-pricking Errors of Four Men.*

Time of experiments.	Pure alcohol.	Claret.	Time of experiments.	Pure alcohol.	Claret.
4.37 and 4.40	2·92	2·11	5.27 and 5.30	2·55	2·30
4.43 and 4.46	2·70	2·18	5.33 and 5.36	2·47	2·36
4.49 and 4.52	2·22	1·90	5.39 and 5.42	2·54	2·29
4.55 and 4.58	2·32	1·68	5.45 and 5.48	2·17	2·18
5.0	alcohol	alcohol	5.51 and 5.54	2·05	1·70
5.3 and 5.6	1·96	1·57	5.57 and 6.0	1·90	1·85
5.9 and 5.12	2·14	1·91	6.3 and 6.6	1·90	1·85
5.15 and 5.18	2·23	1·98	6.9 and 6.12	1·91	1·73
5.21 and 5.24	2·19	2·09	6.15 and 6.18	1·77	1·63

was always taken three hours, or rather more, after food, and the order in which the experiments were made was reversed in two of the four subjects, so as to equalize the effects of practice. The mean results of the experiments are recorded in Table XXIX, and these results are reproduced graphically in Fig. 10. It will be seen that the effects were distinctly greater than in myself, but no exact numerical comparison is possible because of the considerable improvement of skill shown by the students during the course of the experiments. Whilst their average target-pricking error in the last two experiments was only 1·70 mm., or rather less than my own (1·79 mm.), it was 2·52 mm. in the first two experiments, as against a value of 2·05 mm. in myself. The errors which probably would have been made if no

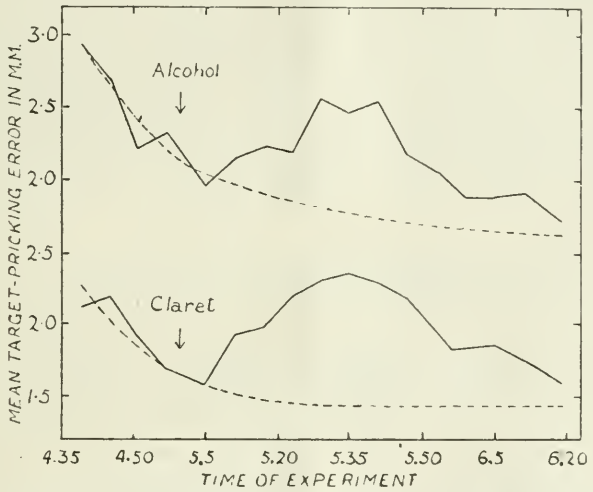

Fig. 10. The Effects of Alcoholic Liquids on the Target-pricking Errors of Four Men.

alcohol had been taken are drawn as dotted lines through the respective curves. These dotted lines are not the same for the two curves, but a reference to the data in Table XXIX will show that it would be incorrect to make them so. It happened that on the days of the experiments with pure alcohol the subjects made considerably greater target-pricking errors than on the days of the claret experiments. In order to obtain a numerical comparison of the effects of the pure alcohol and the claret, one can compare the mean error made at the height of the alcohol effect (viz. from 5.27 to 5.43) with that made in the last 16 minutes of the experiments, when most of the alcohol effect had worn off. The increment of error works out at 35 per cent. in the pure alcohol experiments, and 33 per cent. in the claret experiments. If, on the other hand, the basis of comparison be taken as from 5.3 to 5.13, or just before much alcohol effect had developed, the increment of error works out at 23 per cent. in the pure alcohol experiments, and 33 per cent. in the claret experiments. Probably, therefore, we may conclude that the claret was slightly more toxic than the alcohol.

The four students varied distinctly in susceptibility, one of them (Mr. Dreyer, on whom numerous typewriting experiments have been

recorded) being more susceptible than the average, and one of them less susceptible, whilst the other two were about the average. The experiments made with the fifth student are not included with those made on the other four, as they call for special mention. This student had been stationed for three years, 1915–17, on the West Coast of Africa, and, by reason of the trying climate, had got into the habit of drinking rather heavily. From data which he gave me as to the amount of his mess bills, and the price of whisky, I was able to calculate that he drank between a half and two-thirds of a bottle of whisky a day, on an average, or about 170 c.c. of pure alcohol. His body weight is 10 stone (64 kgm.). He did not start drinking till 11.0 a.m., and took most of the alcohol between meals, and very little of it with food. When he returned to England he resumed temperate habits, and now drinks about three pints of beer a week. He felt some craving for more alcohol for the first three months after his return, but he has no desire whatever for it now. When this student took the usual 30 c.c. of diluted alcohol and 294 c.c. of claret, he showed no increase of target-pricking error whatever, as can be gathered from the upper curve shown in Fig. 11 which records the mean of the two experiments, and the data in Table XXX. A week after these

TABLE XXX.—*The Effect of 30 to 60 c.c. Alcohol on the Target-pricking Errors of a rather Heavy Drinker.*

Times of experiments.	30 c.c. alcohol or claret.	Whisky containing 45 or 60 c.c. alcohol.	Times of experiments.	30 c.c. alcohol or claret.	Whisky containing 45 or 60 c.c. alcohol.
11.37 and 11.40	3·18 } 3·32	2·68	12.33 and 12.36	2·00	1·38
11.43 and 11.46	3·47 }	2·50	12.39 and 12.42	2·00	1·28
11.49 and 11.52	2·98	2·32	12.45 and 12.48	1·85	1·30
11.55 and 11.58	2·92	2·20	12.51 and 12.54	1·95	1·35
12.0	alcohol	alcohol	12.57 and 1.0	1·98	1·35
12.3 and 12.6	2·87 } 2·54	1·83	1.6	2·02	1·15
12.9 and 12.12	2·20 }	1·55	1.12	2·07 } 1·98	1·18
12.15 and 12.18	2·22	1·45	1.18	1·90 }	1·27
12.21 and 12.24	2·13	1·33	1.24	1·90	1·22
12.27 and 12.30	2·07	1·37			

experiments were made, he carried out another experiment in which he drank 45 c.c. of alcohol in the form of whisky diluted to 20 per cent. alcoholic strength. Two days later he made another experiment in which he drank 60 c.c. of alcohol in the form of whisky diluted to 27 per cent. strength. The whisky was taken three hours after food or practically on an empty stomach, but neither dose had a definite effect on neuro-muscular co-ordination. The lower curve in Fig. 11 is

a mean of the two whisky experiments, and though it may be taken to indicate a slight increase of target-pricking error 30 to 60 minutes after drinking the alcohol, the increase is so slight as to be within the limits of experimental error.

The student said that he experienced no subjective sensations of vertigo whatever after drinking the whisky, and certainly his conversation showed no signs of any effect. Hence it follows that a dose of alcoholic liquid which would have induced a state not far removed

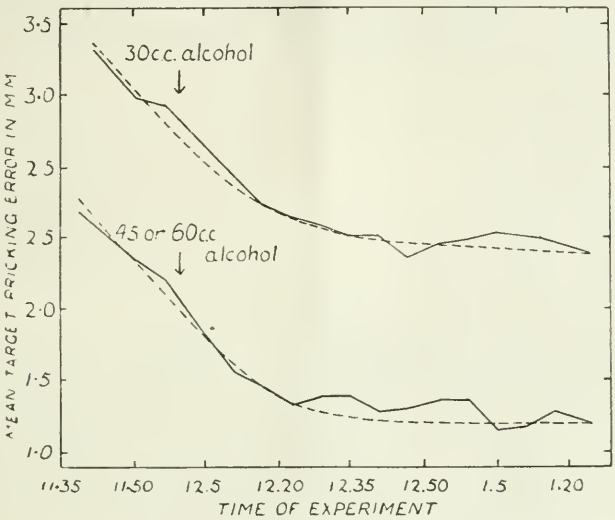

FIG. 11. The Effects of Alcoholic Liquids on the Target-pricking Errors of a rather Heavy Drinker.

from intoxication in myself and in three of the other four medical students, was practically without effect upon him. Apparently his acquired immunity to alcohol had persisted unchanged for a year since he gave up heavy drinking.

Other Experiments upon the Effects of Wine and Spirits.

As it is important to determine whether the adverse effects of moderate quantities of alcoholic liquids are general, Dr. W. C. Sullivan and Capt. M. Greenwood, members of the Advisory Committee, were good enough to make a series of experiments upon themselves and their assistants, and to furnish me with an account of these experiments.

The detailed information here adduced, of the experiments on subjects K., B., and S., is quoted from Dr. Sullivan's account, but the comments on it, which are given at the end, are my own.

Capt. Greenwood's experiments are described and discussed by himself, except that I have, with his permission, abbreviated some of his Tables of figures.

Dr. W. C. Sullivan's Experiments.

"*Subject K.* The method adopted was to type ten times an official note of 54 words, totalling 250 letters, so that with spacing, changing key, and restarting line, the typing of each note involved 315 movements. The time taken for each complete typing was marked with a stop-watch. All typing was done as rapidly as the typist felt to be consistent with general accuracy. The subject is a skilled typist.

The daily routine was as follows:—

Breakfast finished	8.45 a.m.
1st typing	10.0 a.m.
2nd typing	12.15 p.m.
Lunch finished	1.30 p.m.
3rd typing	2.15 p.m.
Tea finished	3.45 p.m.
4th typing	4.0 p.m.

The alcohol on an *empty* stomach was taken at 11.45 a.m., or half an hour before the second typing, whilst the alcohol on a *full* stomach was taken with or immediately after lunch, or three-quarters of an hour before the third typing. The subject did no other typing during the experiment. Being a skilled typist, she did not practise the letter before starting the experiment. The test recorded here lasted for 29 days. For 5 days, viz. from June 17 to 21, the tests were done without alcohol, and again for 4 days at the end, from July 23 to 26. The following quantities of alcoholic liquids were taken:

From June 24 to 28, 13 oz. claret (= 36·7 c.c. alcohol) were taken with lunch.

July 1 to 5, 13 oz. claret (= 36·7 c.c. alcohol) were taken on empty stomach at 11.45 a.m.

July 9 to 12, and 15, 4 oz. port (= 22·0 c.c. alcohol) were taken with lunch.

July 16 to 19, and 22, 4 oz. port (= 22·0 c c. alcohol) were taken on empty stomach at 11.45 a.m.

The results are shown in Tables XXXI to XXXVI. The figures entered opposite each day indicate—in the time column—the average time (in seconds) taken to type the note at each of the several séances of the day; and the figures under 'errors' show similarly the average number of mistakes made in typing the note at each of the séances.

The subject is a moderate drinker, and is not susceptible to alcohol. She found the claret rather too much in bulk, and had great difficulty in drinking the second glass. She felt slightly irritable all the afternoon. At the end of the week, she felt markedly tired. The port caused her no discomfort whatever.

TABLE XXXI.—*First Week—No Alcohol.*

	Time.				*Errors.*			
	10 *a.m.*	12.15 *p.m.*	2.15 *p.m.*	4 *p.m.*	10 *a.m.*	12.15 *p.m.*	2.15 *p.m.*	4 *p.m.*
June 17	53·2	49·7	49·5	46·2	0·5	0·3	0·3	0·1
,, 18	48·8	47·6	48·4	44·2	0·1	0·6	0·7	0·3
,, 19	46·2	45·5	45·5	45·0	0·3	0·0	0·6	0·4
,, 20	44·2	44·2	43·2	45·0	0·1	0·1	0·0	0·8
,, 21	43·4	43·0	44·0	42·6	0·3	0·1	0·6	0·2
Weekly average	47·2	46·0	46·1	44·6	0·26	0·22	0·44	0·36

TABLE XXXII.—*Second Week—Claret after Lunch.*

	Time.				*Errors.*			
	10 *a.m.*	12.15 *p.m.*	2.15 *p.m.*	4 *p.m.*	10 *a.m.*	12.15 *p.m.*	2.15 *p.m.*	4 *p.m.*
June 24	44·0	44·1	47·6	48·0	0·4	0·1	1·3	1·3
,, 25	43·5	42·1	43·8	43·3	0·1	0·5	0·6	0·0
,, 26	42·7	43·4	45·4	44·2	0·1	0·2	0·8	0·5
,, 27	42·7	42·2	44·8	40·7	0·6	0·2	1·1	0·5
,, 28	42·6	43·2	45·9	42·1	0·3	0·4	1·1	0·6
Weekly average	43·1	43·0	45·5	43·7	0·30	0·28	0·98	0·58

TABLE XXXIII.—*Third Week—Claret before Lunch.*

	Time.				*Errors.*			
	10 *a.m.*	12.15 *p.m.*	2.15 *p.m.*	4 *p.m.*	10 *a.m.*	12.15 *p.m.*	2.15 *p.m.*	4 *p.m.*
July 1	41·9	49·7	47·6	42·4	0·5	3·6	2·2	0·4
,, 2	40·8	45·7	45·2	43·9	0·4	1·7	0·3	0·7
,, 3	40·9	44·9	44·9	41·7	0·2	2·5	1·2	0·5
,, 4	41·9	48·8	47·1	44·4	0·7	2·8	1·0	0·3
,, 5	42·4	42·7	45·6	42·9	0·3	1·4	1·5	1·4
Weekly average	41·6	46·4	46·1	43·1	0·42	2·40	1·24	0·66

TABLE XXXIV.—*Fourth Week—Port after Lunch.*

	Time.				*Errors.*			
	10 *a.m.*	12.15 *p.m.*	2.15 *p.m.*	4 *p.m.*	10 *a.m.*	12.15 *p.m.*	2.15 *p.m.*	4 *p.m.*
July 9	41·4	41·9	44·0	42·2	0·4	0·7	0·9	0·9
,, 10	42·5	42·0	41·2	39·7	0·7	0·5	0·5	0·5
,, 11	40·3	48·9	42·3	40·9	0·6	0·9	0·3	0·3
,, 12	40·6	41·1	42·5	41·1	0·4	0·8	0·4	0·5
,, 15	41·8	41·8	42·3	40·0	0·1	0·6	0·5	0·5
Weekly average	41·3	43·1	42·5	40·8	0·44	0·70	0·52	0·54

TABLE XXXV.—*Fifth Week—Port before Lunch.*

	Time.				*Errors.*			
	10 *a.m.*	12.15 *p.m.*	2.15 *p.m.*	4 *p.m.*	10 *a.m.*	12.15 *p.m.*	2.15 *p.m.*	4 *p.m.*
July 16	41·6	42·1	42·7	40·2	0·3	0·7	0·7	0·0
,, 17	40·8	43·1	40·6	41·5	0·6	1·3	0·7	0·0
,, 18	41·6	43·1	43·6	40·5	0·5	1·4	0·5	0·4
,, 19	41·9	44·2	44·5	40·0	0·6	2·0	0·5	0·4
,, 22	43·1	44·7	42·3	40·9	0·5	1·9	0·4	0·6
Weekly average	41·8	43·4	42·7	40·6	0·50	1·46	0·56	0·28

TABLE XXXVI.—*Sixth Week—No Alcohol.*

	Time.				*Errors.*			
	10 *a.m.*	12.15 *p.m.*	2.15 *p.m.*	4 *p.m.*	10 *a.m.*	12.15 *p.m.*	2.15 *p.m.*	4 *p.m.*
July 23	42·9	41·6	43·3	41·4	0·6	0·5	0·4	0·3
,, 24	42·5	42·8	43·4	42·2	0·2	0·2	0·2	0·9
,, 25	40·5	42·9	41·6	41·5	0·2	0·2	0·1	0·3
,, 26	42·7	40·1	43·2	41·7	0·3	0·2	0·0	0·5
Weekly average	42·1	41·9	42·9	41·7	0·32	0·27	0·17	0·50

Subject B. The method adopted was to type a proverb 100 times at each sitting, in groups of 10 sets of the proverb. The proverb consisted of 6 words, totalling 28 letters, so that with spacing, changes of key, and restarting line, the typing of each group involved 344 movements. The time taken for each complete group was marked with a stop-watch. All typing was done as rapidly as the typist felt to be consistent with speed and accuracy. The subject is a skilled typist.

The daily routine was as follows:—

Breakfast finished	9.0 a.m.
1st typing	10.0 a.m.
2nd typing	12.40 p.m.
Lunch finished	2.0 p.m.
3rd typing	2.45 p.m.
Tea finished	4.0 p.m.
4th typing	4.30 p.m.

The alcohol on an *empty* stomach was taken at 12.10 p.m., or half an hour before the second typing, whilst the alcohol on a *full* stomach was taken with or immediately after lunch, or three-quarters of an hour before the third typing. The subject did her ordinary work during the tests. She practised the test for a week before starting the experiment. The tests recorded here lasted over 22 days, and were carried out in the following order:

From June 3 to 7, no alcohol was taken.

June 10 to 14, 13 oz. claret (=36·7 c.c. alcohol) were taken with lunch.

June 18 and 19, July 18, 4 oz. sherry (=22 c.c. alcohol) were taken with lunch.

Aug. 12, 13, 15, 21, and 26, 4 oz. sherry were taken on empty stomach at 12.10 p.m.

Aug. 29 and 30, Sept. 2 and 3, no alcohol was taken.

The subject is practically an abstainer, and is very susceptible to alcohol. She found difficulty in drinking the claret on account of its bulk, but the sherry was less objectionable. Both doses caused severe headache and nausea. The results are shown in Tables XXXVII to XLI.

TABLE XXXVII.—*First Group—No Alcohol.*

	Time.				*Errors.*			
	10 *a.m.*	12.40 *p.m.*	2 45 *p.m.*	4.30 *p.m.*	10 *a.m.*	12.40 *p.m.*	2.45 *p m.*	4.30 *p.m.*
June 3	55·0	53·9	53·9	53·6	2·2	0·9	1·9	1·5
„ 4	51·7	53·5	51·1	53·3	2·3	1·9	1·6	3·4
„ 5	47·7	48·9	48·1	47·5	2·8	3·4	2·8	2·9
„ 6	46·1	49·1	46·6	47·7	2·0	4·8	2·5	1·6
„ 7	48·1	48·8	47·8	45·6	1·4	1·1	2·9	1·7
Average	49·7	50·8	49·5	49·5	2·14	2·42	2·34	2·22

TABLE XXXVIII.—*Second Group—Claret after Lunch.*

	Time.				*Errors.*			
	10 *a.m.*	12.40 *p.m.*	2.45 *p.m.*	4.30 *p.m.*	10 *a.m.*	12.40 *p.m.*	2.45 *p.m.*	4.30 *p.m.*
June 10	47·3	46·5	49·0	46·6	1·9	1·5	4·5	4·0
,, 11	43·4	47·8	46·6	47·9	2·3	3·9	3·3	3·2
,, 12	44·8	45·2	45·2	44·9	3·8	2·8	5·5	7·0
,, 13	44·4	45·1	46·3	45·4	1·7	2·7	6·0	5·0
,, 14	44·5	43·8	44·9	42·4	4·1	4·2	6·0	3·4
Average	44·9	45·7	46·4	45·4	2·76	3·02	5·06	4·52

TABLE XXXIX.—*Third Group—Sherry after Lunch.*

	Time.				*Errors.*			
	10 *a.m.*	12.40 *p.m.*	2.45 *p.m.*	4.30 *p.m.*	10 *a.m.*	12.40 *p.m.*	2.45 *p.m.*	4.30 *p.m.*
June 18	43·9	43·8	46·3	42·6	3·4	3·5	3·8	3·3
,, 19	44·2	43·8	43·9	44·1	2·5	2·2	3·1	1·8
July 18	43·7	44·3	42·9	42·4	2·2	2·0	2·7	2·3
Average	43·9	44·0	44·4	43·0	2·70	2·57	3·20	2·47

TABLE XL.—*Fourth Group—Sherry before Lunch.*

	Time.				*Errors.*			
	10 *a.m.*	12.40 *p.m.*	2.45 *p.m.*	4.30 *p.m.*	10 *a.m.*	12.40 *p.m.*	2.45 *p.m.*	4.30 *p.m.*
Aug. 12	44·8	45·4	45·2	43·9	2·0	4·4	2·1	1·9
,, 13	43·8	44·5	42·9	43·3	1·0	2·7	1·3	1·2
,, 15	43·9	46·2	44·7	43·0	1·5	4·1	2·3	1·4
,, 21	43·1	46·2	43·3	41·8	1·2	3·9	2·3	0·7
,, 26	43·7	45·4	43·5	42·2	1·6	3·6	1·7	2·2
Average	43·9	45·5	43·9	42·8	1·46	3·74	1·94	1·48

TABLE XLI.—*Fifth Group—No Alcohol.*

	Time.				*Errors.*			
	10 *a.m.*	12.40 *p.m.*	2.45 *p.m.*	4.30 *p.m.*	10 *a.m.*	12.40 *p.m.*	2.45 *p.m.*	4.30 *p.m.*
Aug. 29	44·3	45·4	45·1	44·0	1·9	1·5	1·6	1·1
,, 30	44·6	44·4	45·2	45·0	1·5	1·3	1·1	0·9
Sept. 2	44·1	44·2	44·4	44·0	1·2	1·4	0·3	0·9
,, 3	47·6	45·6	44·3	45·0	1·7	2·1	0·7	1·3
Average	45·1	44·9	44·7	44·5	1·57	1·57	0·92	1·05

Subject S. The method adopted was to type the alphabet 100 times at each sitting, the typing being done in sets of 10 alphabets, and the time of typing each set being taken with a stop-watch. The unit for calculating error and speed was thus the set of 10 alphabets. A pause of half a minute was made between each set. The subject typed as rapidly as he felt to be consistent with general accuracy. He is an amateur and uses a faulty method of typing, employing only one finger of each hand—viz. the index finger of the right hand, and the middle finger of the left, the latter being used to strike the 9 letters on the left side of the keyboard. This method was originally adopted casually, and has become habitual.

There were 4 typing séances on each day of the test, viz. at 10.30 a.m., 1.0 p.m., 3.30 p.m., and 5.0 p.m. The experiment, of which the results are here summarized, extended over 13 days between the dates of June 5 and June 25. On the first 4 days, no alcohol was taken. On the other 9 days, 2½ oz. brandy (= 26·25 c.c. alcohol) diluted with an equal part of water were taken, either at 12.40 p.m. —i. e. on an empty stomach, 20 minutes before the 1.0 p.m. typing—or at 2.45 p.m.—i. e. after a light lunch, and three-quarters of an hour before the 3.20 typing. Tests on empty stomach and after food were made on alternate dates. The results are shown in Tables XLII to XLIV. The figures entered opposite each date in the time columns indicate the average times (in seconds) taken to type a set of 10 alphabets at each of the several séances of the day; and the figures under 'errors' show similarly the average number of mistakes made in typing the set of alphabets at each of the séances. At the bottom of each Table, the average results are expressed in percentage relation to the record at 10.30 a.m. taken as the normal of the day."

TABLE XLII.—*Period before Commencement of Alcohol Test.*

Date.	*Time.*				*Errors.*			
	10.30 *a.m.*	1 *p.m.*	3.30 *p.m.*	5 *p.m.*	10.30 *a.m.*	1 *p.m.*	3.30 *p.m.*	5 *p.m.*
June 5	72·6	73·9	72·8	72·7	2·3	3·4	2·9	2·8
,, 6	69·3	66·8	68·2	67·4	4·6	2·2	1·9	2·9
,, 7	68·4	66·4	66·4	69·4	3·5	3·6	4·2	3·3
,, 8	66·8	67·7	69·3	67·3	4·0	5·5	5·7	4·1
Average	69·3	68·7	69·2	69·2	3·6	3·7	3·7	3·3
Average percentage result	100	99	100	100	100	103	103	92

TABLE XLIII.—*Alcohol on Empty Stomach.*

$2\frac{1}{2}$ oz. Brandy with Equal Part of Water at 12.40.

Date.	*Time.*				*Errors.*			
	10.30 *a.m.*	1 *p.m.*	3.30 *p.m.*	5 *p.m.*	10·30 *a.m.*	1 *p.m.*	3·30 *p.m.*	5 *p.m.*
June 12	63·2	66·1	66·5	65·4	4·1	6·1	8·2	5·8
,, 14	60·8	64·9	63·2	60·4	3·7	7·8	7·3	6·1
,, 19	60·0	60·1	58·3	60·4	2·9	3·4	3·3	4·2
,, 24	58·4	60·2	57·4	58·7	5·4	7·7	4·0	3·8
Average	60·6	62·8	61·3	61·2	4·02	6·25	5·70	4·97
Average percentage result	100	104	101	101	100	155	142	124

TABLE XLIV.—*Alcohol after Food.*

$2\frac{1}{2}$ oz. Brandy with Equal Part of Water at 2.45.

Date.	*Time.*				*Errors.*			
	10.30 *a.m.*	1 *p.m.*	3.30 *p.m.*	5 *p.m.*	10.30 *a.m.*	1 *p.m.*	3.30 *p.m.*	5 *p.m.*
June 11	68·1	68·8	70·3	67·3	5·9	4·9	5·2	5·2
,, 13	61·4	64·4	62·2	65·8	2·9	5·6	6·1	7·2
,, 17	62·3	59·9	62·4	62·6	5·8	4·1	5·9	4·2
,, 21	59·3	58·3	59·5	59·8	4·2	2·9	3·1	2·4
,, 25	56·6	56·2	57·7	57·1	2·8	2·6	3·9	3·4
Average	61·5	61·5	62·4	62·5	4·32	4·02	4·84	4·48
Average percentage result	100	100	101	102	100	93	112	104

Comments by H. M. V. These experiments are specially valuable, in that two out of the three series were made by skilled typists. The average effects produced in subject K. by drinking claret are shown in the upper curves of Fig. 12. They correspond with the investigations previously described, and show that the consumption of claret

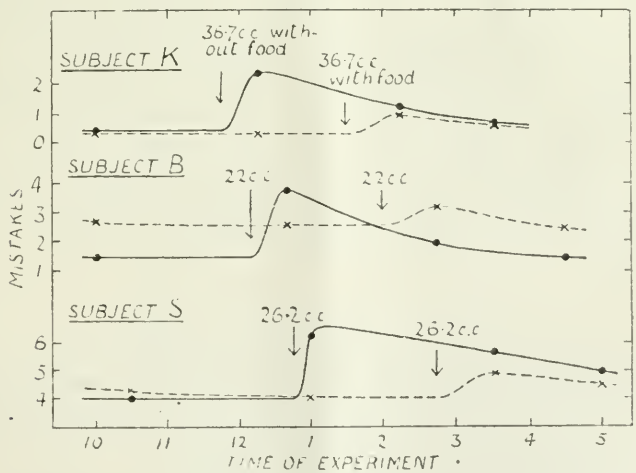

FIG. 12. Effects of Alcoholic Liquids on Subjects K., B., and S.

with food had less than half as much effect on the number of mistakes as its consumption without food. The effect on the typing time was quite marked, as this time was increased 12 per cent. when the claret

was taken without food, and 6 per cent. when it was taken with food. Though subject K. is a moderate drinker and not susceptible to alcohol, the effects of the claret without food on typing time and mistakes persisted to some extent for three and three-quarter hours. The quantity of port consumed contained less than two-thirds as much alcohol as the claret (i. e. 22 c.c. as against 36·7 c.c.), and, in correspondence with this fact, the port without food was found to influence the typing to about the same extent as the larger quantity of claret taken with food. Port taken with food had no appreciable effect upon the typing, or the conclusion arrived at in the target-pricking experiments is confirmed, viz. that for every individual there exists some moderate dose of alcoholic liquid which is without appreciable influence on neuro-muscular co-ordination. It does not follow, of course, that such a dose is without effect on the more complex nervous processes of the brain.

In subject B. the effects of consumption of sherry, with and without food, are shown in the middle curves of Fig. 12. It will be seen that the effectiveness of the wine taken without food was more than twice as great as of that taken with food. The quantity of alcohol contained in the sherry was the same as in the port consumed by subject K., and hence it follows that subject B. was considerably more susceptible than K., in whom the port was without effect. Subject B. also made a series of experiments in which she took 13 oz. of claret (=36·7 c.c. alcohol) with food. This caused her mistakes to increase from 3·02 up to 5·06, whilst the same amount of claret caused K.'s mistakes to increase from 0·28 up to 0·98. With such differences in the scale of errors made under normal conditions, it is impossible to say which of the two subjects was most affected, for though the absolute increase of mistakes was three times as great in B. as in K., the *percentage* increase was not a third as great.

The experiments made by subject S. show that whilst the consumption, on an empty stomach, of brandy containing 26·25 c.c. of alcohol increased the typing errors 55 per cent., it increased them only 12 per cent. (or 20 per cent. in comparison with the average errors made at 1 p m.) when taken with food. The experimental results are shown graphically in the lowest curves of Fig. 12. The dose was rather a small one for a man, hence the effect on the mistakes was only moderate, though it persisted to a considerable extent for four hours in the foodless experiments. The typing time was increased 4 per cent. in the foodless experiments, and 1 per cent. in those with food.

Capt. M. Greenwood's Experiments.

"The experiments were carried out in a fashion similar to that described by Dr. Vernon, but the routine followed and the general conditions were modified in various particulars. Two sets of observations were made; the first was concerned with typewriting trials, the second with work upon an adding machine.

Typewriting Experiments. The machine used was a Blickensderfer Typewriter, the stroke of which is appreciably heavier than that of a standard machine. I have used such a machine for many years, but am neither a quick nor an accurate operator. The task selected was a passage consisting of nine Latin hexameter lines containing

TABLE XLV.—*Typing Experiments by M. G.*

Number of days on which experiments were made, and dates.	Experiments shortly before dinner.						Food taken at dinner—	Experiments shortly after dinner.					
	Slow typings.		Fast typings.		Mean.			Slow typings.		Fast typings.		Mean.	
	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.		Time.	Mistakes.	Time.	Mistakes	Time.	Mistakes.
11 (May 6–17)	99·7	2·1	84·9	4·1	92·3	3·1	without alcohol.	100·6	1·7	86·0	3·6	93·3	2·6
6 (May 18–30)	95·2	1·1	82·9	3·5	89·1	2·3	with 1 glass port (18·5 c.c. alcohol).	96·4	1·3	84·2	4·3	90·3	2·8
4 (June 3–7)	95·2	1·3	81·4	4·1	88·3	2·7	without alcohol.	96·3	1·5	80·9	4·3	88·6	2·9
3 (June 8–14)	95·3	1·8	81·5	3·4	88·4	2·6	with 2 glasses port (37 c.c. alcohol).	93·7	2·1	82·5	6·5	88·1	4·3
5 (June 17–21)	92·1	1·1	80·2	3·6	86·2	2·4	without alcohol.	95·4	1·2	82·3	2·6	88·8	1·9

355 letters, spaces, or stops, while 18 further movements were needed for striking capitals and moving the paper carrier. Each day's experiments consisted of typing the passage eight times, four times before dinner and four times after dinner. Each set of four typings comprised (*a*) a first *slow* typing, the passage being written down at about the pace I usually adopt for letter writing, (*b*) a *fast* typing, i. e. one made at a rate which seemed subjectively a good deal faster than (*a*) but not so much faster that I had any difficulty in striking the keys, (*c*) was a repetition of (*a*), and (*d*) was a repetition of (*b*). Hence each series comprised two 'slow' and two 'fast' trials. The actual time at which the before-dinner series was carried out varied, but was usually between 8.30 and 8.45 p.m. (summer time) and always within a few minutes of dining. The after-dinner series was arranged to commence from 30 to 45 minutes after the alcohol had been drunk.

Alcohol was taken in the form of port wine of known strength; either one or two glasses were drunk, the actual quantities of absolute alcohol taken being 18·5 and 37 c.c. On the non-alcohol evenings I drank tea with my dinner, either two or three teacupfuls of an ordinary infusion without sugar. I adopted this practice because the disadvantage of using a caffein-containing beverage on the control evenings seemed outweighed by the advantage of preserving the normal routine, it being my regular practice to drink either a glass of wine or some cups of tea with my evening meal.

The result of the whole series of experiments, which extended from May 6 to June 21, are set out in Table XLV.

A scrutiny of this Table shows that, whether one considers speed or average mistakes, the first alcohol series, where 18·5 c.c. (one glass of port) were taken, is not differentiated from the general level; on the strength of these experiments it would be impossible to say that such a quantity of alcohol affected either speed or accuracy. The case is altered when we come to the larger quantity of 37 c.c., and I have compared the experiments when this quantity of alcohol was drunk with the means of the previous and succeeding non-alcohol series (after-dinner observations), paying attention to the probable errors. The results of the test are shown in Table XLVI. It will be seen

TABLE XLVI.—*Differences between the Means of Experiments with 37 c.c. of Alcohol and those of the Control Periods, (June 3–7 and 17–21).*

After Food Series.

	Time.	*Errors.*
1st. typing (slow)	-1.5 ± 2.3	$+0.49 \pm 0.53$
2nd. „ (fast)	$+0.8 \pm 1.8$	$+2.91 \pm 0.97$
3rd. „ (slow)	-2.8 ± 1.9	$+1.6 \pm 0.60$
4th. „ (fast)	$+0.8 \pm 1.9$	$+3.22 \pm 0.86$

that in no case is the difference between speeds of significance having regard to the probable errors, but in both of the 'fast' typing trials the alcohol series shows an increase of mistakes nearly thrice the probable error of the difference. Hence it seems incontestable that

two glasses of port wine did cause a decided deterioration in the quality of the work done.

Since in these experiments, which are evidently the only practically important ones in my typing series, there was so little difference in the speeds of corresponding tests, the direct comparison of mistakes is sufficiently instructive; taking mean values of the four trials, the deterioration in the alcohol series as compared with the average of preceding and succeeding series is expressed by an increase of nearly 80 per cent. in the number of mistakes. This result agrees reasonably with Dr. Vernon's general average increase of 69 per cent. when 30 c.c. of alcohol were taken with food, but there are differences of detail between our findings, for while Dr. Vernon saw the maximum effect in the slower typings, I find the reverse. A not improbable explanation of this divergence in detail is that my 'slow' rates represent a routine of work performance which is very familiar to me; that is to say, I have for years used a typewriter and at about the same rate, hence typing at or about this rate is a habit ingrained and not easily disturbed. On the other hand, the 'fast' rates are not normal to me but specially acquired for these experiments, and liable consequently to be disturbed by drug action or otherwise with greater facility.

I think it is of importance to take account of the interruption of habit in experiments of this kind. I suppose most sedentary workers lead regular lives, particularly with respect to the routine of their meals. I have, for certainly ten years, been accustomed to drink a small quantity of wine at dinner, but I cannot recall ever taking more than a single glass of a fortified wine *when I intended to do any work after dinner*. It is a matter for consideration whether the fact that (in the 37 c.c. experiments) my routine was broken through may not have influenced the result. While a single glass of port wine produces in me no subjective effects save a slight increase of well-being, two glasses lead to an appreciable vertigo. The fact, however, that the deteriorating effect in any case is more accentuated at the rapid rates of typing, where there is less leisure for introspection than at the slow rates, is possibly significant.

Adding-machine Experiments. The Burroughs adding machine, the instrument employed, is provided with a series of keys arranged in nine parallel rows. In the model used in our experiments each row consists of nine keys; the highest row is of nine 9's, the second row of nine 8's, and so on. To operate the machine one depresses the appropriate keys with the fingers of the left hand, and the required numbers having been thus set upon the key-board, the addition is performed by pulling back with the right hand, and then letting fly, a lever at the side of the keyboard. The differences between the technique of this machine and that of typewriting are considerable. The keys are only depressed by the fingers of the left hand (in our practice only the index, middle and ring fingers are used), the other hand being reserved for operating the lever. The actual physical work, although slight, is greater than in typing, entirely on account of the manipulation of the lateral lever, the depression of the keys themselves being easier than on a typewriter keyboard and needing little impact. The keys being set very close together, it is easy to strike the key adjacent to the one intended.

The task chosen was to reproduce 123456789 thirty times, involving 270 movements to depress keys and 30 operations of the setting lever. At first it was found a little difficult to keep count, the number actually recorded often proving to be 29 or 31, but this error became rare after a little practice. The test appears to me to reproduce very well the conditions of light lathe work in factories or of several operations in cartridge-case making. A number of fine co-ordinated muscular movements are necessary ; the physical energy needed is slight while the intellectual demands are negligible. The task is in fact very monotonous. At first, experiments were carried out at various hours of the day, but those reported upon in this paper are confined to two daily series : (1) the early series carried out after lunch, (2) the late series carried out a quarter of an hour to half an hour after tea (5 p.m.), at which meal two or two and a half cups of tea were drunk. In the alcohol-with-food experiments, claret was taken at lunch, the volume of claret drunk being 150 c.c., or rather less than a quarter of a bottle, and containing 15·3 c.c. of alcohol. In the without-food experiments, 190 c.c. of claret were drunk containing 19·4 c.c. of alcohol. This latter quantity contained approximately the same volume of alcohol as the one glass of port wine taken in the typing experiments, and was adopted after the apparently slight efficacy of the smaller dose with food had shown itself in the results. In the fasting experiments the alcohol was drunk at the normal hour for food and the tests were made half an hour later. Table XLVII is a record of the experiments made on M. G.

TABLE XLVII.—*Adding-machine Experiments by M. G.*

Number of days on which experiments were made, and dates.	Time and conditions of experiments.	Mean of two slow experiments.		Mean of two fast experiments.		Mean of slow and fast experiments.	
		Time.	Errors.	Time.	Errors.	Time.	Errors.
10 (May 1–21)	After lunch without alcohol	75·7	1·5	66·7	3·4	71·2	2·4
	After tea without alcohol	76·0	1·4	67·7	5·5	71·8	3·4
6 (May 22–29)	After lunch, with 150 c.c. claret (= 15·3 c.c. alcohol)	73·9	1·7	64·1	5·1	69·0	3·4
	After tea without alcohol	72·3	2·3	62·4	3·7	67·4	3·0
5 (May 30–June 6)	After lunch without alcohol	75·6	1·4	64·2	3·8	69·9	2·6
	„ tea „ „	74·5	1·0	61·9	3·8	68·2	2·4
6 (June 7–14)	Early in afternoon, ½ hr. after taking 190 c.c. claret (= 19·4 c.c. alcohol) without food	71·1	2·0	62·4	7·2	66·8	4·6
	After tea without alcohol	73·0	0·4	62·3	2·6	67·7	1·5
5 (June 17–21)	After lunch without alcohol	70·0	1·5	63·5	3·7	66·8	2·6
	„ tea „ „	68·0	0·5	62·0	3·0	65·0	1·8

It will be seen that series of experiments without alcohol were made before and after the alcohol experiments. If the alcohol experiments with food be compared against a mean of the non-alcohol experiments made before and after, the deterioration—measured in terms of mistakes—amounts to 42 per cent., whilst a similar comparison in the fasting experiments shows a deterioration of 74 per cent. This latter figure is of the same order of magnitude as the deterioration experienced in the typing series when twice the volume of alcohol was taken but with a meal. The result is therefore in agreement qualitatively with those of Dr. Vernon and other investigators, testifying to the specially unfavourable action of alcohol taken on an empty stomach. Quantitative comparison is naturally excluded by the variations of other conditions (time of day, nature of task, etc.)

Table XLVIII shows the differences between the means of the time and errors observed in the alcohol experiments and in the control periods. The probable errors have been computed by the aid of the appropriate standard deviations determined from the whole of the experiments, excepting those of the early afternoons following the drinking of alcohol.

TABLE XLVIII.—*Differences between the Means of Experiments with 15·3 c.c. and 19·4 c.c. of Alcohol and those of the Control Periods.*

	Speed of experiment.	*Time.*	*Errors.*
15·3 c.c. alcohol with food	1. slow	-1.8 ± 1.67	0 ± 0.49
	2. fast	$+1.5 \pm 1.25$	$+2.0 \pm 0.74$
	3. slow	$+0.1 \pm 1.76$	$+0.5 \pm 0.34$
	4. fast	-1.3 ± 1.14	$+1.5 \pm 0.84$
19·4 c.c. alcohol without food	1. slow	-1.2 ± 1.56	$+0.5 \pm 0.46$
	2. fast	-1.6 ± 1.16	$+5.0 \pm 0.72$
	3. slow	$+0.6 \pm 1.63$	$+0.5 \pm 0.33$
	4. fast	-1.2 ± 1.15	$+1.8 \pm 0.82$

I think that the close concordance between the adding-machine series and the typing experiments strengthens the conclusions mutually. Two further sets of experiments were carried out by my colleagues C. M. T. and H. M. W. The observations were confined to a comparison of the effects of alcohol (150 c.c. of the claret) taken with food.[1] C. M. T.'s experiments comprised one week with alcohol and the weeks before and after without alcohol. The experiments agreed in results with those of M. G., for the second and fourth, or the rapidly executed tests, showed an increase of mistakes, the difference of the fourth tests being more than thrice the probable difference. The two slow trials were not materially affected by alcohol.

H. M. W., being obliged to leave London on official business before the experiments were completed, her observations only covered a week

[1] Neither lady was in the habit of drinking wine at lunch.

without alcohol and the following week when alcohol was taken at lunch; consequently the effect of practice should favour the experiments done with alcohol. The series showed a deterioration (measured by the average number of mistakes) in the two quickly executed tests, but in one of these the difference was but little larger than its probable error. The two slow trials were unaffected. The four sets of observations, viz. typing and adding tests by M. G., and adding tests by H. M. W. and C. M. T., agree very well with one another and support the following conclusions:

1. Small doses of alcohol, well within the limits of what would be deemed by all moderation, do not sensibly affect the speed of performance of such semi-automatic operations as typing a memorized passage or setting down and adding a row of figures on a mechanical calculator, but gravely depreciate the accuracy of performance.

Two glasses of port wine in a person accustomed to drink a glass of wine have this effect when the wine is taken with food. Less than this is sufficient to produce a result if taken on an empty stomach.

2. Should the task set be very familiar to the subject, the above conclusion does not hold. Such small doses of alcohol did not exert any measurable effect upon the number of mistakes in either a typing or adding test made with a speed of performance to which the subject had become familiarized by long practice.

None of our experiments bring out any effect upon the slow addings or typings, experiments which were made at a speed to which we were quite accustomed.

3. A corollary of 2 is that we cannot confirm Dr. Vernon's observation attesting the particularly unfavourable effect of alcohol upon the first of a series of experiments performed under its influence. For the reason just given, this does not involve any contradiction between the two sets of experiments. We had not realized beforehand the possible importance of this habit factor, and in order to test the point as to an inferiority of first trials it would have been necessary to reverse the order and to have made the series run fast, slow, fast, slow, instead of the other way round.

From the practical standpoint, these results seem to me to emphasize the importance of Dr. Vernon's general conclusion that moderate doses of alcohol affect the accuracy of semi-automatic work more than a casual observer might suppose, while the way in which this effect seems accentuated in work performed under relatively novel conditions is much what ordinary experience would lead us to expect.

Lastly, as to the experimental method, I think that the irregularity of the time equivalents of mistakes and the seeming impossibility, at any rate with short series of experiments, of arriving at a quantitative measure of the effects of practice, suggest that in future experiments it would be advisable to perform the tests at as uniform a rate as possible, measurements not being made until a training period has elapsed sufficient in length to render subsequent improvement with practice very slight."

IV. General Conclusions.

The experimental evidence which has been adduced concerning the action of alcohol on manual work and neuro-muscular co-ordination is considerable in bulk, but, by reason of its multiple origin, is rather disconnected. As it has been impossible to present it in such a manner as to indicate the broad conclusions which may be deduced, it is worth while to attempt to summarize such conclusions now.

We have seen that experiments were made upon eight men and five women altogether, and that all of them, with one doubtful exception, showed some reaction to the very moderate doses of alcohol and alcoholic liquids employed. This reaction was invariably in the direction of diminished control of the muscles, as was proved by the increase in the number of typing and adding-machine mistakes, by diminished typing speed, and by increased error in pricking a target. There was never any initial improvement, even of brief duration, such as Kraepelin sometimes observed in reaction-time experiments, and in simple mental work such as reading aloud. At the same time it was found that in some of the subjects a small dose of alcohol, if taken with food, might induce no measurable reaction whatever. This non-reactive dose amounted to one glass of port (= 18·5 c.c. alcohol) in M. G. and to 4 oz. port (= 22 c.c. alcohol) in K., but it must have been considerably less than this in the more susceptible subjects, such as K. D. V. and B. When taken on an empty stomach, alcohol was found to be about twice as toxic as when taken with food, and consequently even 15·3 c.c. of alcohol (in the form of claret) caused some reaction in M. G., whilst 11·2 c.c. of pure alcohol, suitably diluted, caused a considerable reaction in K. D. V. A dose of 20 c.c. of alcohol caused a very small increase in the typing mistakes of H. M. V. and N. B. D., but 22 to 26·2 c.c. of alcohol (taken as port, sherry, or brandy) caused a considerable reaction in K., B., and S. However, individuals vary enormously in susceptibility, for it was found that a student who had, a year previously, been rather a heavy drinker, showed little or no reaction to a dose of whisky containing 45 or 60 c.c. of alcohol.

The types of manual work investigated are not very typical ones, as they involve quicker movements than those made in the majority of industries, but on the other hand the target-pricking experiments necessitated slower and more deliberate movements than those usually met with. Hence it may be concluded that the effects produced by alcohol in these very different types of muscular movement would apply equally to the movements of intermediate speed which are required in many classes of manual work. In all work with the hands requiring skill and delicacy of muscular control, one may be confident that, whilst strictly moderate quantities of alcoholic liquors, taken by persons accustomed to alcohol, may not appreciably reduce manual skill, they can seldom if ever improve it. Moreover, such persons continually run the risk of finding their manual skill quite appreciably reduced if they happen to take their alcohol on an empty stomach instead of a full one. It would be far better for them to avoid the risk altogether by postponing their consumption of alcohol till the day's work is over.

The target-pricking experiments agree with the typing experiments in indicating that very moderate doses of alcohol are without appreciable effect. The experiments with larger doses, if confirmed on other subjects, yield a result of some practical importance. They showed that, above a certain limit, the increasing lack of neuromuscular co-ordination varies directly with the amount of alcohol consumed. There is no sudden increase of effect produced by a comparatively small additional dose. In other words, the man who, when convicted of drunkenness, pleads the unexpected effects of a single extra glass has no scientific support for his contention. He must have been nearly drunk before the final glass was taken. The toper who occasionally finds that the quantity of alcohol which he can usually carry with comfort has led to unexpected intoxication has probably made some change in the conditions under which he consumed his drink. He may have consumed it a longer time than usual after his last meal, and thereby have taken it on an empty stomach instead of a full one, or he may have consumed it more quickly, and so, for a few fatal minutes, have obtained a greater concentration of alcohol than usual in his blood.

In the preface to the book on Alcohol issued by the Advisory Committee, Lord D'Abernon propounds a number of questions upon which further knowledge is desirable, and some of these questions can be answered in part from the experimental evidence adduced. Firstly, he asks to what extent pure alcohol differs in its action from alcoholic beverages of corresponding strength. The reply is that it differs comparatively little. Different subjects do not all react alike, but on an average it appeared that wine and spirits are rather more toxic than pure ethyl alcohol of equal quantity and strength. As would be expected, the difference was not at all marked, for the quantity of higher alcohols and other narcotics present in matured wine and spirits is very small compared with that of ethyl alcohol. No experiments were made with immature spirits.

Another question concerned the effects of dilution. Experiments in which the dilution of alcohol varied from 5 per cent. to 40 per cent., or roughly in proportion as they vary in beer and in neat spirits, showed that the difference was not great. A 5 per cent. solution had about three-fourths as much effect on typing errors as 20 and 40 per cent. solutions, whilst dilute brandy, containing 10 per cent. of alcohol, had likewise about three-fourths as much effect on target-pricking errors as neat brandy containing 37 per cent. of alcohol. The difference of effect probably depends almost entirely on the rate of absorption. Thus 30 c.c. of alcohol, in 40 per cent. solution, has a volume of only 75 c.c., but in 5 per cent. solution it has a volume of 600 c.c., and it would be highly improbable that the alimentary canal could absorb this large volume of liquid as quickly as the small one. If it cannot, then the concentration of alcohol in the blood cannot reach so high a level, and the maximum toxic effect must likewise be less.

Another question concerns the effect of drinking alcohol with and without food. Upon this point a very large amount of evidence has been adduced, as it is one which has been curiously ignored by most previous investigators. As a rule, no mention whatever is made by

them as to the time which elapsed between the consumption of food and the consumption of the experimental dose of alcohol, though we have seen that this is a matter of extreme importance. All experiments ought to be made, so far as possible, on a full stomach or an empty one, and not under some intermediate and ill-defined conditions, such as would ensue if the alcohol were taken about two hours after food. The assumption made in the present experiments, that the stomach is practically empty three hours after food is taken, is not always correct, and it would have been better to have waited for four hours, but as a rule it would have been inconvenient to wait so long, seeing that the experiments lasted one and a half to two hours after the alcohol d been consumed.

The influence of food on the toxic action of alcohol depends on several factors. The food dilutes the alcohol considerably, but, more important than this, it greatly delays its absorption. The alcohol gets well mixed with the stomach contents, and thereby is prevented from coming into such frequent and intimate contact with the gastric mucous membrane as when it is taken without food. Again, the mixture of food and alcohol remains much longer in the stomach than does alcohol without food, and it is probable that the gastric mucous membrane absorbs alcohol considerably more slowly than the intestinal mucous membrane. If the food contains much fat, the fat not only delays the passage of the food from stomach to intestine, but it dissolves part of the alcohol, and this alcohol can only be absorbed when the fat is itself digested and absorbed. Thus I found that when a dose of 60 c.c. of alcohol was taken with a fatty meal, it produced less effect on typing than if it were taken with a fatless meal. On the other hand, the effect continued to a marked extent for three and three-quarter hours or more, though it had disappeared in the fatless experiments.

V. Summary.

The influence of alcohol on manual work and on neuro-muscular co-ordination was investigated in eight men and five women. In seven of the subjects observations were made on the accuracy and speed of typewriting: in three, on the accuracy and speed of working an adding machine, and in six, on the accuracy with which a target could be pricked.

In the typewriting experiments a memorized passage was typed frequently before and after the alcohol, and it was found that as a rule the speed was but little diminished, but the number of mistakes made was increased two- or even four-fold. It was found to be possible to correct for the variable speed, and obtain a measure of the alcohol effect in terms of mistakes only. The possible influence of mental impressions on the result was excluded by typing every day for alternate weeks with and without alcohol. As some of the series of experiments lasted for six weeks, and were consistent throughout, the effects observed can be accepted with confidence.

Alcohol produced some effect in all of the individuals tested by the typing and adding-machine methods. The degree of effect depended largely on whether the alcohol was taken on an empty

stomach or with food, for on an average it was about twice as toxic under the former conditions as under the latter. In the foodless experiments, one subject made 88 per cent. more typing mistakes after she drank 11·2 c.c. of alcohol. Another subject increased his adding-machine mistakes 74 per cent. after taking claret containing 19·4 c.c. of alcohol; another increased her typing mistakes 156 per cent. after drinking sherry containing 22 c.c. of alcohol.

In some subjects a moderate dose of alcoholic liquid, taken with food, produced no measurable reaction. Such a non-reactive dose amounted to one glass of port (= 18·5 c.c. alcohol) in a male subject, and to 4 oz. of port (= 22 c.c. alcohol) in a female subject.

The effect reached its maximum half an hour after taking alcohol on an empty stomach, and might completely disappear in two hours. When the alcohol was taken with food, the effect was slightly longer in reaching its maximum.

When alcohol (30 c.c.) was taken in 5 per cent. strength, the effect produced was about three-fourths as great as when it was taken in 20 per cent. or 40 per cent. solution. A similar difference was observed when taking diluted brandy (10 per cent. alcohol) and neat brandy (37 per cent. alcohol).

In the target method, rows of dots, made on squared paper fixed vertically at arm's length, were pricked at 3-minute intervals before and after the alcohol. The average distance of a prick from the centre was about 1·8 mm., but after taking 30 c.c. of alcohol the target-pricking error increased 12 per cent.; after taking 37·5 c.c. it increased 43 per cent., and it continued to increase in arithmetical progression with the dose of alcohol till it was 132 per cent. above the normal when 60 c.c. were taken. The influence of alcohol on target-pricking errors developed and disappeared synchronously with its influence on typing errors.

Experiments made on five subjects with claret and pure alcohol of equal alcoholic strength showed that claret was slightly the more toxic. Diluted brandy had slightly less effect than claret, but neat brandy slightly more.

One subject who, a year before, had been rather a heavy drinker, showed little if any reaction, even after drinking whisky containing 45 or 60 c.c. of alcohol. He was tested by the target method, and took the whisky three hours after food.

Table I.—*Normal Week.*

Date.	Mean times of typing.												Mean of slow and fast typings.	
	9.11 a.m.				6.51 p.m.				10.2 p.m.					
	Slow typing.		Fast typing.		Slow typing.		Fast typing.		Slow typing.		Fast typing.			
	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.
Feb. 8	127·7	1·7	120·3	3·0	129·0	1·5	122·0	4·5	128·7	1·5	124·2	3·9	125·3	2·7
,, 9	122·7	1·7	117·3	2·3	128·3	0·3	121·3	2·3	124·7	1·3	119·2	3·3	122·4	1·9
,, 10	127·1	1·3	119·0	3·0	122·3	1·7	117·7	3·0	127·0	1·0	120·0	3·5	122·2	2·3
,, 11	128·7	2·0	120·0	3·7	[124·7	1·0	118·1	3·0]	127·0	0·5	118·0	3·7	122·7	2·3
,, 12	127·7	1·3	119·7	2·3	124·7	0·7	115·3	0·3	125·3	3·0	116·3	3·0	121·5	2·1
,, 13	128·7	2·0	113·0	2·2	119·0	1·0	114·0	3·0	123·0	1·3	112·0	5·3	118·3	2·5
Mean	127·1	1·7	118·2	2·8	124·7	1·0	118·1	3·0	126·0	1·4	118·4	3·8	122·1	2·3

No typings were made at 6.51 p.m. on February 11, the data inserted being the mean of the results obtained on other days. On February 8 typings were made at 8.14 instead of 6.51 p.m.

TABLE II.—*30 c.c. Alcohol with Food at 7.15 p.m.*

Date.	Mean times of typing.																Mean of slow and fast typings.	
	9.15 a.m.				6.41 p.m.				9 p.m.				10.40 p.m.					
	Slow typing.		Fast typing.		Slow typing.		Fast typing.		Slow typing.		Fast typing.		Slow typing.		Fast typing.			
	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.
Feb. 14	119·3	0·3	111·7	5·7	119·0	1·0	110·0	3·2	123·6	2·1	111·8	4·5	123·7	0·7	113·7	2·8	116·6	2·6
,, 15	120·7	1·3	109·0	2·5	113·0	1·0	107·3	2·3	121·0	1·7	106·7	3·8	124·3	1·7	114·0	2·0	114·5	2·0
,, 16	117·7	0·3	112·7	3·7	124·3	0·3	110·0	3·7	117·3	1·8	112·0	5·7	123·0	0·7	116·3	3·0	116·7	2·4
,, 17	120·3	1·0	117·7	2·2	118·7	0·5	108·7	3·0	126·3	2·7	109·7	2·8	120·0	1·3	110·7	3·7	116·5	2·2
,, 18	117·7	0·8	112·3	3·7	120·3	1·3	107·7	3·8	119·7	1·0	111·3	3·3	117·7	1·5	111·3	3·5	114·8	2·4
,, 19	121·3	0·2	107·3	3·3	122·7	1·0	107·3	1·8	119·0	2·3	109·0	4·3	125·7	3·0	110·7	3·2	115·4	2·4
,, 20	118·3	1·0	113·3	2·8	115·3	0·0	106·0	2·0	114·0	1·3	113·0	4·8	120·0	1·5	107·0	2·5	113·4	2·0
Mean	119·3	0·7	112·0	3·4	119·0	0·7	108·1	2·8	120·1	1·8	110·5	4·2	122·1	1·5	112·0	3·0	115·4	2·3

TABLE III.—*30 c.c. Alcohol without Food at 5 p.m.*

Date.	Mean times of typing.																Mean of slow and fast typings.	
	4.50 p.m.				5.52 p.m.				7.6 p.m.				9.14 p.m.					
	Slow typing.		Fast typing.		Slow typing.		Fast typing.		Slow typing.		Fast typing.		Slow typing.		Fast typing.			
	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.
Feb. 21	111·7	1·0	106·7	3·3	116·3	4·7	110·7	5·7	116·7	0·8	105·7	3·5	115·3	1·2	10 5·3	3·3	111·1	2·9
,, 22	113·3	1·8	101·3	2·5	120·0	4·5	111·0	5·5	118·0	1·7	106·0	3·7	115·0	1·0	108·3	3·2	111·6	3·0
,, 23	106·0	0·7	101·3	3·7	114·3	3·7	108·0	7·1	114·3	1·0	105·7	1·8	120·3	1·1	109·7	4·8	110·0	3·0
,, 24	115·7	1·5	104·0	2·3	116·0	2·3	109·7	6·0	108·0	1·3	101·7	4·3	119·0	1·8	107·7	3·7	110·2	2·9
,, 25	108·3	1·1	99·7	3·5	113·0	1·8	103·0	3·1	111·0	2·1	105·3	4·1	113·3	0·8	97·3	1·5	106·4	2·3
,, 26	110·3	1·0	101·7	2·8	115·0	2·5	107·7	6·8	115·7	1·1	104·7	3·8	114·0	1·5	109·0	3·0	109·8	2·8
,, 27	106·3	0·8	101·0	3·0	114·0	2·5	106·3	4·1	114·0	2·0	104·0	3·5	114·0	2·0	105·0	3·3	108·1	2·7
Mean	110·2	1·1	102·2	3·0	115·5	3·1	108·1	5·5	114·0	1·4	104·7	3·5	115·8	1·3	106·0	3·3	109·6	2·8

The last typing on February 24 was made at 10.48 p.m., and on February 25 at 8.11 p.m.

TABLE IV.—*60 c.c. Alcohol with Food at 7.15 p.m.*

Date.	Mean times of typing.																Mean of slow and fast typings.	
	9.10 a.m.				6.38 p.m.				8.51 p.m.				10.42 p.m.					
	Slow typing.		Fast typing.		Slow typing.		Fast typing.		Slow typing.		Fast typing.		Slow typing.		Fast typing.			
	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.
Feb. 28 *	(107·7)	(0·5)	(103·0)	(1·8)	(111·0)	(1·7)	(103·3)	(2·0)	(111·0)	(2·8)	(105·0)	(3·0)	(101·3	(2·3)	(109·3	(2·0)	(107·6	(2·0)
Mar. 1	110·3	1·5	105·7	3·7	107·7	2·1	101·7	5·5	112·7	5·0	105·0	4·8	111·0	2·0	105·3	5·0	107·4	3·7
,, 2	111·7	2·7	105·7	4·1	112·7	2·7	103·0	2·8	110·7	1·8	107·3	5·5	108·7	2·7	104·3	3·5	108·0	3·2
,, 3	113·1	1·7	102·2	2·8	110·0	1·5	104·5	3·2	112·1	4·3	106·1	8·3	108·5	2·1	101·9	4·7	107·3	3·6
,, 4	113·6	3·7	107·1	4·0	108·7	1·7	99·9	4·7	109·2	4·5	106·6	5·3	112·6	2·8	101·9	3·7	107·3	3·8
,, 5	108·3	2·1	99·8	4·0	108·7	1·5	99·3	3·7	111·9	5·3	100·0	3·3	107·3	3·0	98·7	5·7	104·3	3·6
,, 6	113·3	1·5	101·8	4·3	109·1	1·3	102·3	2·8	111·7	4·8	108·5	6·3	112·5	3·0	102·1	3·0	107·7	3·4
Mean	111·7	2·2	103·7	3·8	109·5	1·8	101·8	3·8	111·4	4·3	105·4	5·6	110·1	2·6	102·4	4·3	107·0	3·5

* On February 28, 45 c.c. of alcohol were taken instead of 60 c.c., so the data of this day are not averaged with the rest.

TABLE V.—*Normal Week.*

Date.	Mean times of typing.																Mean of slow and fast typings.	
	9.10 a.m.				6.42 p.m.				8.58 p.m.				10.42 p.m.					
	Slow typing.		Fast typing.		Slow typing.		Fast typing.		Slow typing.		Fast typing.		Slow typing.		Fast typing.			
	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.	Time.	Mistakes.
Mar. 7	110·7	2·0	103·5	3·3	110·7	1·5	99·2	2·8	113·5	1·1	105·3	3·8	109·9	0·7	106·0	2·7	107·3	2·2
,, 8	113·3	3·1	106·9	5·3	106·4	0·7	98·8	3·5	112·6	1·0	101·2	1·7	108·5	1·7	106·3	4·5	106·8	2·7
,, 9	109·7	1·5	105·4	2·8	109·6	2·0	100·9	2·0	108·2	1·3	104·5	3·8	110·4	0·0	108·0	3·1	107·1	2·1
,, 10	112·9	1·0	101·1	2·5	108·8	1·0	106·7	2·7	111·5	1·0	100·5	2·3	111·4	1·0	105·7	1·8	107·3	1·7
,, 11	113·9	2·1	106·9	4·1	109·0	1·3	101·0	1·1	107·7	0·7	102·2	3·3	111·9	1·8	103·7	0·8	107·0	1·9
,, 12	112·7	1·5	99 7	1·8	106·1	0·5	98·2	2·1	111·1	0·7	100·5	2·8	112·2	1·0	103·3	3·5	105·5	1·7
,, 13	112·4	2·3	99·3	3·0	111·7	0·8	101·7	2·5	108·5	0·7	99·8	2·7	112·6	1·8	107·0	2·7	106·6	2·1
Mean	112·2	1·9	103·3	3·3	108·9	1·1	100·9	2·4	110·4	0·9	102·0	2·9	111·0	1·1	105·7	2·7	106·8	2·1

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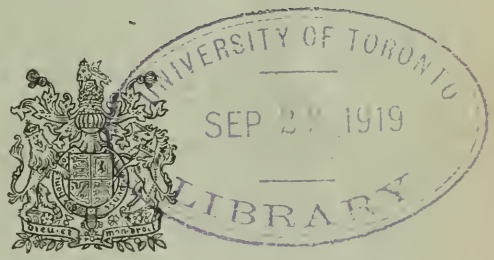
MEDICAL RESEARCH COMMITTEE

Reports of the Special Committee upon Pathological Methods

THE REACTION OF MEDIA



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REPORTS

OF THE

SPECIAL COMMITTEE UPON PATHOLOGICAL METHODS

V.—THE REACTION OF MEDIA

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(*Secretary*).

In April, 1917, the Medical Research Committee invited the following special Committee to consider how far it may be practicable and desirable to obtain the standardization of routine pathological methods, and to report to them. The special Committee were empowered to co-opt additional members for particular divisions of their subject.

Colonel J. G. Adami, C.B.E., M.D., F.R.S., C.A.M.C. (*Chairman*).
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Professor William Bulloch, M.D., F.R.S.
Captain S. R. Douglas, I.M.S. (*Secretary*).

The Report now presented was prepared by a sub-committee constituted as follows:

Professor J. W. H. Eyre, M.D. (*Chairman*).
P. P. Laidlaw, M.A., B.Ch.
C. G. L. Wolf, M.D.
Captain S. R. Douglas, I.M.S. (*Secretary*).

THE REACTION OF MEDIA

Modern work in bacteriology has shown that among the factors influencing growth the reaction of the medium is an important one.

Many observers have pointed out that although some bacteria will grow in media having a wide range of reaction, there are certain reactions at which optimum growth takes place. On the other hand, there are certain bacteria which require a more limited range, so that to obtain the best possible growth the reaction of the medium employed must be accurately defined within these limits.

Until a few years ago, the reaction of a medium was expressed in terms of the amount of a standard normal or decinormal acid which would be necessary to bring the medium to neutrality, using litmus paper or phenolphthalein solution as an indicator. This method served a very useful purpose in adjusting media of similar composition to a more or less arbitrary standard which trial had shown to be generally suitable for growth. Later experience has demonstrated that these titration tests do not give the true reaction when carried out in media of different compositions, and, what is more disadvantageous, tests carried out by individual workers, under what are presumed to be identical conditions, lead to widely divergent results. This is shown in a table given by Clark in which eight careful observers, using the same apparatus and the same medium, obtained results varying between 0·7 c.c. and 5·1 c.c. of a $\frac{N}{40}$ NaOH solution in titrating a 5 per cent. peptone solution. It is clear that the reactions of these neutralized peptones cannot have been the same, and that errors of this size may be serious.

If under these carefully controlled conditions the variations were so great, it can be safely assumed that workers in different laboratories would encounter even wider discrepancies when attempting a similar series of experiments.

The causes of the errors in titration are partly due to the personal equation of the manipulator, his colour sense, &c., but for the most part to the fact that the end point is not sharp. Near the end point of the titration there is a zone where the addition of acid or alkali does not produce a striking change in the colour of the indicator (see Buffers, p. 7).

The true reaction of any fluid is determined by the amount of hydrogen or hydroxyl ions which are present in it. For theoretical and practical reasons which are not for the moment important, the reaction of a fluid is therefore expressed by the concentration of hydrogen ions which it contains. Using this standard to check the results of the older titration method an

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example of wide departure from what was expected may be quoted. A 'neutral' plain broth was prepared, using the titration method to determine its reaction. It was found to have a P_H of 8·4. This, as will be shown later, is a difference between $1{\cdot}0 \times 10^{-7}$ (= neutrality) and $0{\cdot}04 \times 10^{-7}$, or a difference in hydrogen ion concentration of 1 to 25. It is evident that errors of this magnitude may readily give rise to difficulty, or mistakes, when the bacteriologist is dealing with organisms which only grow well within somewhat narrow limits of reaction. It would appear, therefore, that the determination of the true reaction of a medium should be adopted in place of the titration figure now in common use, provided that this can be done simply and expeditiously.

In accurate determinations of hydrogen ion concentrations the hydrogen electrode is used.

The principle involved in this determination is that if a solution containing a certain concentration of hydrogen ions is in contact with a metal saturated with hydrogen, a difference of electrical potential is set up due to the transfer of hydrogen ions from the place of saturation (the electrode) to the place where the hydrogen ions are in lesser concentration (the solution). Depending on the concentration of hydrogen ions in the solution, this difference will vary, and can be measured. From this measurement the concentration of hydrogen ions in the solution can be readily calculated. The details of the method, in so far as bacteriological media are concerned, will be found in papers by Walpole and by Barendrecht.

In ordinary laboratory practice very accurate results may be obtained by a colorimetric method, which is comparatively simple in its application. This is the method advocated and described later (pp. 12–15).

Nevertheless it must be emphasized that the determination of the hydrogen ion concentration by the hydrogen electrode is the final court of appeal.

The simple considerations on which the true acidity of a solution are based may be stated as follows:

The acidity is expressed in terms of the weight of free hydrogen ions present in a litre of solution. This is entirely analogous to the ordinary expression of the strength of solutions as 'normal' or 'decinormal', *but only* when the following considerations are taken into account.

In a normal solution of hydrochloric acid one has 36·5 grams of the acid in solution, of which 35·5 grams consist of chlorine and one gram is hydrogen. In the case of hydrogen ion concentration the anions (chlorine in the case of hydrochloric acid) are neglected, and the kation, hydrogen only, is referred to.

Hence, in a normal solution of hydrochloric acid there ought to be 1 gram of hydrogen per 1,000 c.c. The concentration is therefore 1/1000. As the concentrations of hydrogen ions dealt with in biology are very much smaller than this, it was found to be more convenient to express the normality in terms of

negative powers of ten. Thus in dealing with 0·1 normal solution, the expression is 1×10^{-1}; 0·01 normal $= 1 \times 10^{-2}$; 0·001 normal $= 1 \times 10^{-3}$, &c.

In a solution of hydrochloric acid, the dissociation of the hydrogen and chlorine into the respective H and Cl ions is nearly complete. If it were complete, a 0·001 normal solution would have a hydrogen ion concentration of 1×10^{-3}. This is not strictly the case, for a certain amount of the acid is not dissociated, and therefore the amount of hydrogen ions is less than 1×10^{-3}. Investigation has shown that the real concentration is $0{\cdot}97 \times 10^{-3}$, because only 97 per cent. of the acid is completely dissociated.

The difference in the case of hydrochloric or any other 'strong' acid is not great, but in dealing with organic acids, such as are frequently encountered in biological work, a much greater difference will be found. This is due to the fact that these acids dissociate much less completely than hydrochloric acid. For example, in the case of 0·001 normal acetic acid, which ought to have a hydrogen ion concentration of $0{\cdot}97 \times 10^{-3}$ if it were as completely dissociated as hydrochloric acid, experiments have shown that the real concentration is only $0{\cdot}136 \times 10^{-3}$, that is to say, acetic acid has only $\frac{0{\cdot}97}{0{\cdot}136}$ or approximately one-seventh of the amount of hydrogen ions contained in a similar solution of hydrochloric acid.

The method of expressing the hydrogen ion concentration directly has proved cumbrous and inconvenient, for two numbers are involved in the expression, viz. the actual amount and the minus power to which this is raised. It is not easy to use this expression in constructing curves except by keeping the power constant, and then the figures become so great that a very large graph is necessary for their exposition. The second difficulty is that the hydrogen electrode method of determining the reaction, on which all these data are based, does not give the results directly in this form. On this account Sörensen proposed designating both figures in terms of a negative logarithm, and the custom has been generally followed. The minus sign is understood, but is generally omitted. Hence 1×10^{-5} becomes 5·0; $1 \times 10^{-6} = 6{\cdot}0$, &c. This value is known as the 'hydrogen exponent' and is usually written P_H.

The only difficulty for the beginner is in translating the actual hydrogen ion concentration into P_H when the amount is a fraction. For example, it is quite easy to understand that 1×10^{-5} is equivalent to P_H 5·0, but the process of transforming $2{\cdot}0 \times 10^{-5}$ into P_H is not so simple. The method of conversion is as follows:

$$1{\cdot}00 \times 10^{-5} \text{ or } P_H = 5{\cdot}00$$
$$2{\cdot}00 \times 10^{-5} \text{ or } P_H = 4{\cdot}7,$$

for the logarithm of $2{\cdot}0 = 0{\cdot}3$. This added to $-5{\cdot}00 = -4{\cdot}70$, or, the minus sign being always understood, $= 4{\cdot}7$.

To take a practical example. The hydrogen ion concentration

of 0·001 acetic acid is $1{\cdot}36 \times 10^{-4}$. The logarithm of $1{\cdot}36 = 0{\cdot}133$. Hence the P_H of this solution is $0{\cdot}133 - 4{\cdot}00 = 3{\cdot}867$.

The following table, taken from the paper of Hurwitz, Meyer, and Ostenberg, gives the relation between some constantly recurring hydrogen ion exponents and the actual concentration.

P_H.	Hydrogen ion concentration.	P_H.	Hydrogen ion concentration.
6·4	$4{\cdot}0 \times 10^{-7}$	7·5	$0{\cdot}32 \times 10^{-7}$
6·6	$2{\cdot}5 \times 10^{-7}$	7·6	$0{\cdot}25 \times 10^{-7}$
6·8	$1{\cdot}6 \times 10^{-7}$	7·7	$0{\cdot}20 \times 10^{-7}$
7·0	$1{\cdot}0 \times 10^{-7}$	7·8	$0{\cdot}16 \times 10^{-7}$
7·1	$0{\cdot}8 \times 10^{-7}$	8·0	$0{\cdot}10 \times 10^{-7}$
7·2	$0{\cdot}63 \times 10^{-7}$	8·2	$0{\cdot}063 \times 10^{-7}$
7·3	$0{\cdot}5 \times 10^{-7}$	8·4	$0{\cdot}040 \times 10^{-7}$
7·4	$0{\cdot}4 \times 10^{-7}$		

Two features must be noted when dealing with such minus logarithms. One is that the actual amount of hydrogen ions increases as the P_H decreases. That is to say, $P_H = 7{\cdot}0$ represents a more acid solution than $P_H = 8{\cdot}0$. The second point is that as these are logarithms the amounts represented are logarithmic and not simple quantities ; thus, as will be seen by a reference to the above table, a P_H of 7·7 represents a solution containing twice the number of hydrogen ions contained in a solution with $P_H = 8{\cdot}0$. Similarly, a P_H of 3·0 indicates that the solution has ten times as many hydrogen ions as a solution of $P_H = 4{\cdot}0$.

Neutrality.

It has been ascertained by experiment that the total concentration of hydrogen ions existing in the purest water at 20° C. $= 1 \times 10^{-7}$. Hence the hydrogen exponent of water is 7·00. This must represent neutrality, because in this liquid the hydrogen and hydroxyl ions are equally balanced, any dissociation of water which takes place gives H− and OH+ in equal quantity. The optimum growth of most bacteria takes place in this region. The attempts which have been made to fix a neutral point in bacteriological media by means of titration have usually resulted in a fluid which is on the alkaline side of neutrality. Whether this is more advantageous for growth than strict neutrality has not been determined. We do know, however, that the reaction of the blood fluids is in the region of $P_H = 7{\cdot}5$.

All bacteria, in fact all forms of living matter, produce acids in the course of growth. With animals, lactic acid is one of the principal products. Bacteria also produce this acid, and, in addition, formic, acetic, propionic, butyric, and other higher acids are formed. These lead to the acidification of the medium. This is a familiar experience with B. coli, one of the characteristics of which is to produce so much acid in a medium containing certain carbohydrates that neutral red changes colour.

The accumulation of acids is one of the main causes of the cessation of growth. It can be shown that not only do bacteria stop growing when they have produced sufficient acids to give rise to a certain hydrogen ion concentration, but that a medium

originally adjusted to such a reaction absolutely inhibits growth. The same medium made slightly more alkaline will permit growth.

The question of acid production and its effect on the growth of bacteria is important, for one of the factors in securing an abundant growth is to have the initial reaction of the medium at the proper level, and a second is to prevent the acids produced from effecting a change in the reaction of the fluid.

Regulators or Buffers.

An abrupt change in the reaction of the medium when acids are developed during the growth of an organism is prevented by the presence of certain compounds which have the property of taking up hydrogen ions. This property is possessed by proteins, amino acids, and certain salts such as the soluble phosphates, carbonates, borates, &c. All these compounds are called 'regulators' or 'buffers'. They take up hydrogen ions so that the addition of moderate quantities of acids makes a comparatively small change in the reaction of the fluid.

The so-called 'buffer effect' has been experienced by all who have titrated bacteriological media. The usual experience is that 'a sharp end point' is not obtained. The colour changes gradually as alkali or acid is added, and the full and pure colour of the indicator is not given until what is apparently a large excess of reagent has been added. This is quite different from the sharp change which is observed when a strong alkali and acid are titrated against one another, using the same indicator. This gradual colour change in the indicator when used in organic media is due partly to the circumstance that an indicator has a considerable range of reaction through which it changes colour; thus phenolphthalein commences to acquire a pink colour at $P_H = 8{\cdot}00$, but does not develop its fullest colour until $P_H = 10{\cdot}0$. Various indicators change at different ranges: methyl orange, for example, changes between $P_H = 3{\cdot}00$ and $P_H = 4{\cdot}7$. Intermediate between these we have a number of indicators whose range of change has been worked out. It is due to Clark, and those who have worked with him, that the following series of indicators has been investigated which have colour changes between $P_H = 1{\cdot}0$ and $P_H = 10{\cdot}0$:

List of Indicators and their Range.

Indicator.	Range.
Thymol sulphonephthalein, acid range (Thymol Blue)	1·2–2·8
Tetrabromphenol sulphonephthalein (Bromphenol Blue)	2·8–4·6
Orthocarboxybenzene azodimethylaniline (Methyl Red)	4·4–6·0
Dibromcresol sulphonephthalein (Bromcresol Purple)	5·2–6·8
Dibromthymol sulphonephthalein (Bromthymol Blue)	6·0–7·6
Phenol sulphonephthalein (Phenol Red)	6·8–8·4
Orthocresol sulphonephthalein (Cresol Red)	7·2–8·8
Thymol sulphonephthalein, alkaline range (Thymol Blue)	8·0–9·6

The description of these indicators and the method of using them will be found in Clark's papers referred to in the bibliography at the end of this report.

One of the most useful is phenol sulphonephthalein, or, as it is usually called, 'phenol red'. The colour changes are best appreciated between $P_H = 7{\cdot}2$ and $P_H = 8{\cdot}0$. It is in this region that the most useful reactions for bacteriological media occur.

Within the range $P_H = 7{\cdot}2$ to $P_H = 8{\cdot}0$ the tint of a solution to which a little phenol red has been added is a measure of the hydrogen ion concentration of that solution, and hence its true reaction. While phenol red is suitable for this range of reactions, other indicators must be used when other regions of acidity are investigated.

The initial reaction of a bacteriological medium may be determined and controlled, in terms of hydrogen ions, by adopting the following procedure. A solution of definite and known hydrogen ion concentration is prepared, and to this a small amount of a suitable indicator is added. The tint of this forms the standard to which the medium must be brought by titration. A precisely similar proportion of indicator is added to a small sample of the medium and the tint compared with that of the standard, care being taken that similar thicknesses of solution are viewed in both cases. Acid or alkali is added from a burette until the colours of test solution and standard match. The yellow-brown colour of the original untreated medium is readily and accurately compensated, in making the colour match, by interposing a tube of untreated medium between the standard tube and the source of light.[1]

With a series of solutions of known hydrogen ion concentration and a suitable series of indicators any initial reaction may be imparted to a medium within the range $P_H = 1{\cdot}0$ to $P_H = 10{\cdot}0$.

Further, the final hydrogen ion concentration resulting from bacterial growth may be rapidly found by merely adding indicator and comparing the tint with the series of standards. The whole process is simple, rapid, and accurate.

The Preparation of Solutions of definite known Hydrogen Ion Concentration.

For range of reaction between $P_H = 6{\cdot}5$ and $P_H = 8{\cdot}0$ a suitable series of standard solutions may be made from a solution of disodium hydrogen phosphate—the 'sodium phosphate' of the British pharmacopoeia—and acid potassium phosphate.

As the proportion of the dihydrogen potassium phosphate increases, the hydrogen ion concentration of the solution increases owing to partial hydrolysis of the salt.

[1] There are certain salt and protein errors which occur with some indicators which cannot be disregarded when small differences are being noted. A discussion of these errors will be found in a paper by Clark and Lubs, *J. Bact.*, 1917, 2, 123.

The method of employing phosphate solutions of a definite hydrogen ion concentration and phenol red as an indicator, as standards for bacteriological work, was introduced by Hurwitz, Meyer, and Ostenberg on the basis of the previous work of Levy, Rowntree, and Marriott, who had determined the reserve alkali of the blood in this way. Hurwitz and his co-workers compensated for the colour of the medium by placing tubes of media in a line with the standard solution. In this way a very perfect compensation is easily accomplished. It is the same method which Walpole had previously employed in a different way. The standard solutions of Hurwitz, Meyer, and Ostenberg have been since employed by Cole and Onslow and by Clark. Cole and Onslow use two standard solutions instead of one, and Clark has developed media based on the reaction between potassium phthalate and acid potassium phosphate and hydrochloric acid or sodium hydroxide. With these reagents standard hydrogen ion solutions may be prepared ranging from $P_H = 2{\cdot}11$ to $P_H = 8{\cdot}02$.

The solutions necessary for preparing a set of standards of definite hydrogen ion concentration are:

1. A 1/15 molecular solution of acid potassium phosphate KH_2PO_4.
2. A 1/15 molecular solution of disodium phosphate Na_2HPO_4 $2\,H_2O$.
3. A 0·02 per cent. solution of phenol red.

The following are the directions for preparing these solutions:

1. A pure acid potassium phosphate is prepared by recrystalizing the salt two or three times from distilled water. It is dried first between filter paper and finally in a water oven at 100° C.

Of this salt, 9·078 grams are weighed out and dissolved in about 500 c.c. of distilled water contained in a litre flask; 45·5 c.c. of the indicator solution are added and the volume made up to 1,000 c.c. with distilled water.

2. The dihydrate of disodium phosphate has been found to be the most suitable for preparing a standard solution. It is made as follows: A quantity of the crystalline sodium phosphate of the pharmacopoeia, which should be of the purest quality, is placed in a flat dish in a layer not more than 1–2 cm. deep. It is covered with paper to protect from dust and allowed to stand for about two weeks at room temperature. The room should be dry; for when the atmosphere is very humid, the salt may not lose the necessary quantity of water. The salt should be turned over with a spatula every second day, and any of the larger lumps crushed. At the end of two weeks the salt is transformed into a snow-white granular substance having the composition Na_2HPO_4, $2\,H_2O$. A check may be made of the loss of weight during the last few days by weighing out about a hundred grams with an accuracy of 0·1 gram and weighing again in the course of a couple of days. The two weights should agree to 0·1 gram. It is advisable to have the water content of the salt

checked by analysis. This may be done by determining the loss in weight when the salt is dried to constant weight at 98° C. in a water oven. The loss should equal 20·2 per cent. of the weight of the dihydrate. A 1 per cent. solution should give a red colour with a few drops of phenolphthaleine. Of the dihydrate so prepared, 11·876 grams are weighed out and dissolved in about 500 c.c. of distilled water contained in a litre flask. 45·5 c.c. of the indicator solution are added and the volume made up to 1,000 c.c.

3. The 0·02 per cent. solution of phenol red is prepared by dissolving 0·1 gram of phenol sulphonephthalein in about 100 c.c. of distilled water to which 10 c.c. of N/10 sodium hydroxide solution have been added. The solution may be hastened by gentle heating. About 300 c.c. of water are added, and the alkaline solution of the indicator is exactly neutralized with 10 c.c. of N/10 hydrochloric acid. The volume is then made up to 500 c.c.

The Preparation of Standards.

The standard phosphate solutions are based upon the following data taken from Sörensen's table. The mixtures have the corresponding hydrogen ion exponent set against them.

cc. N/15 Na_2HPO_4.	cc. N/15 KH_2PO_4.	−log. (H) or PH.
2	8	6·24
3	7	6·47
4	6	6·64
5	5	6·81
6	4	6·98
7	3	7·17
8	2	7·38
9	1	7·73
9·5	0·5	8·04

From this table by means of interpolation the following table of mixtures has been constructed. These figures have been checked by actual determinations with the hydrogen electrode, and are found sufficiently correct for practical purposes.

c.c. of 1/15 molecular Na_2HPO_4 solution.	Diluted with 1/15 molecular KH_2PO_4 solution to	P_H.
38·0	100	6·6
43·5	100	6·7
49·5	100	6·8
55·5	100	6·9
61·0	100	7·0
66·5	100	7·1
72·0	100	7·2
76·5	100	7·3
80·5	100	7·4
84·0	100	7·5
86·5	100	7·6
89·0	100	7·7
91·3	100	7·8
93·0	100	7·9
94·5	100	8·9

The apparatus necessary for preparing the standard tubes of definite hydrogen ion concentration are:

1. Standard burette, 50 c.c. in 1/10ths.
2. Standard 100 c.c. flasks.
3. Tubes to contain the standard solutions.

These are made from 'cordite' tubes.[1] They are thoroughly cleaned by boiling with distilled water, rinsed out several times with water, and dried in the water oven. They are then drawn out in the blow-pipe flame about 8 cm. from the sealed end so that a constriction is formed about 3 mm. in diameter through which they can subsequently be filled.

4. Small capillary funnel made from a test-tube by drawing out a neck less than 3 mm. in diameter and about 15 cm. long.

The method of making the mixtures is as follows:

The volume of the disodium phosphate solution is measured into a carefully cleaned 100 c.c. graduated flask from the burette, and the volume made up exactly to 100 c.c. with the acid potassium phosphate. The mixture so obtained will have the corresponding hydrogen exponent.

The 'cordite' tubes are then filled with this solution, using the small capillary funnel. It is advisable to place a few small crystals of thymol in the tubes to prevent any bacterial growth. The tubes are numbered and the proper P_H indicated upon them, and are sealed in the blow-pipe and are ready for use. They should be kept in the dark when not in use.

As the dihydrate of sodium phosphate is somewhat difficult to prepare, and the dihydrogen potassium phosphate crystallizes with ease, an alternative method is given for preparing solutions of definite hydrogen ion concentration from the latter salt.

The solutions necessary are:

1. A 1/5 normal solution of dihydrogen potassium phosphate containing phenol red. This is made by weighing out 13·616 grams of that salt. This is dissolved in about 300 c.c. of boiled distilled water. To the solution is added 90·6 c.c. of a 0·02 per cent. solution of phenol red. The mixture is then made up to 500 c.c.

2. A N/10 solution of sodium hydroxide.

From these two solutions the following mixtures are made up:

N/5 KH_2PO_4	N/10 NaOH	Water to	P_H
25	17·80	100	6·6
25	23·65	100	6·8
25	29·63	100	7·0
25	35·00	100	7·2
25	39·50	100	7·4
25	42·80	100	7·6
25	45·20	100	7·8
25	46·80	100	8·0

[1] 'Cordite tubes' are specially selected tubes of hard white glass which have a uniform thickness of wall and external diameter. They are used in certain colour reactions in the routine testing of cordite. Test-tubes of good quality may also be used, provided that a careful selection is made, so that they are all of the same measurements. The cordite tubes may be obtained from Baird and Tatlock, Cross Street, Hatton Garden, London, E.C

This is done by measuring out 25 c.c. of the phosphate solution with a pipette into a standard 100 c.c. flask. The requisite amount of N/10 sodium hydroxide solution as given in the table is added from a burette and the volume of the mixture made up to 100 c.c. with distilled water.

It should be thoroughly appreciated that the task of making up sets of tubes containing standard solutions of definite hydrogen ion concentration is one in which scrupulous care must be observed. It is absolutely essential that the salts used are of the highest purity. At the present time this degree of purity is not to be found in commercial preparations, and therefore the directions regarding purification and control by analysis must be carried out. In all cases, where possible, it would be better to entrust the preparation of the solutions to a chemist, rather than to attempt to make them in the bacteriological laboratory. For the chemist, the making of the solutions is a comparatively simple matter.

The Adjustment of the Reaction of Media.

It is usually desired to prepare a medium which has a reaction in the neighbourhood of $P_H = 7{\cdot}0$ to $P_H = 7{\cdot}5$. Whatever the reaction of the medium may be before it is adjusted, it is useful to add so much alkali in the form of a normal sodium hydroxide or a normal sodium carbonate solution that a drop of the medium on a piece of coralline paper gives a faint rose tint.[1] A medium which is made alkaline to this extent usually has a reaction somewhat more alkaline than strict neutrality ($P_H = 7{\cdot}0$). The reaction of the medium may then be accurately adjusted.

The apparatus and reagents necessary for adjusting the reaction are:

1. Set of tubes containing solutions of known P_H with a definite concentration of indicator.

2. Colour comparator. This consists of a rack to hold the tubes. In its earliest and simplest form it had places for two sets of tubes (Hurwitz, Meyer, and Ostenberg). A later form which is recommended has places for three sets of tubes (Cole and Onslow) (see fig. 1), or a rack may be made to contain a larger series of tubes (see fig. 2).

3. Microburette. This may be improvised from an accurate 1·0 c.c. or 2·0 c.c. bacteriological pipette divided into 0·01 or 0·02 c.c. A fine tip is attached to the lower end with rubber tubing and the delivery of the liquid controlled with a pinch-cock.

4. Bacteriological pipette to deliver 0·5 c.c. and ordinary pipette of 5·0 c.c. capacity.

[1] Coralline (rosolic acid) paper is prepared by dipping thin filter paper or glazed paper into a 0·5 per cent. solution of the indicator in 50 per cent. alcohol. The strips of paper are then dried in the air and kept in a stoppered bottle. In using this paper the earliest change of colour can be detected by allowing the wet paper to come into contact with a piece of dry, white filter paper, which clearly shows the faintest pink colour.

5. Clean cordite tubes.

6. Phenol red solution, 0·01 per cent., made by diluting the 0·02 per cent. solution with an equal volume of water.

7. Twentieth normal sodium hydroxide solution, made by taking 500 c.c. of 1/10 normal NaOH, 91 c.c. of 0·01 phenol red, and making up to 1,000 c.c. with water.

Five c.c. of the medium are measured out into one of the cordite tubes, and 0·5 c.c. of the 0·01 per cent. solution of phenol red are added. This is put in place 3 in the rack. In places 2 and 6 are put the standard tubes of the reaction between which it is desired to adjust the medium. In place 4 is put a tube of distilled water. In places 1 and 5 are put tubes containing the medium without the addition of indicator.

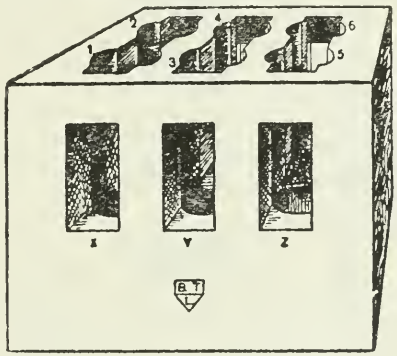

Fig. 1.

In this way the light passing through the standard tubes 2 and 6 traverses tubes containing uncoloured medium in 1 and 5, while the tube containing medium and indicator in 3 is backed by a layer of water. The conditions under which the light comes through the layers of liquid in all three sets of tubes are thus identical.

Suppose that a reaction of $P_H = 7{\cdot}3$ is desired. Standard tubes 7·2 and 7·4 are placed in spaces 2 and 6. It is easy to see from inspection of the standard tubes in the rack whether the medium is more alkaline or more acid than is wished. If the medium is more acid than the standard 7·2 it will be necessary to add alkali to tube 3 until the tint of this tube comes between the tints 7·2 and 7·4. To do this, the 1/20 normal NaOH is added slowly from the microburette until the tint is between 7·2 and 7·4. After the addition of each small quantity of 1/20 normal alkali the contents of tube 3 are well mixed before comparison.[1]

It has been suggested that the 5 c.c. of medium should be

[1] For strict accuracy the same quantity of standard alkali should be added at the same rate to tubes 1 and 6, so as to compensate for any colour change of the natural pigment of the medium. Colour changes of this type are especially marked in the case of media made from vegetables.

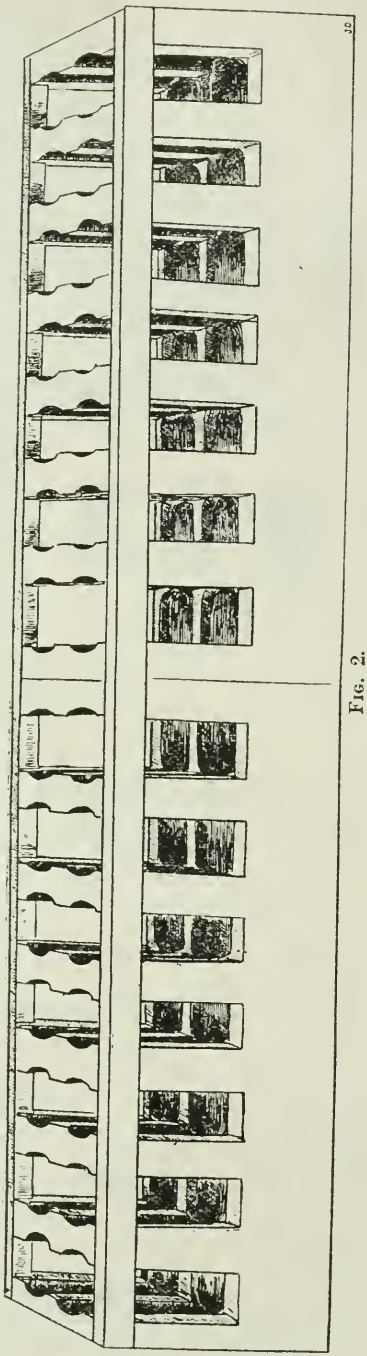

FIG. 2.

gently boiled for thirty seconds and cooled rapidly before being titrated. This to a certain extent compensates for changes which take place on sterilization, and is, on the whole, a useful procedure.

Knowing the amount of N/20 alkali which is necessary to bring the contents of tube 3 to the required tint, it is easy to calculate how much normal alkali will be necessary to bring a large volume of the medium to the requisite hydrogen ion concentration.

For example:

2,000 c.c. of a broth are made slightly alkaline to coralline by the addition of normal alkali. A broth is required of $P_H = 7{\cdot}4$.

In order to bring the tint of a tube containing 5 c.c. of the medium to a tint which will match the standard 7·4 tube, 0·32 c.c. of N/20 alkali are required.

Then the amount of normal alkali which will be required to be added to 2,000 c.c. of broth will be:

$$\frac{2{,}000}{1} \times \frac{1}{20} \times \frac{0{\cdot}32}{1} \times \frac{1}{5} = 64{\cdot}0 \text{ c.c.}$$

It will be noted that no allowance is made for the dilution of the broth by the 64·0 c.c. of alkali added. If the amount is not large, this error may be neglected for practical purposes.

Increase in Hydrogen Ion Content on Sterilization.

All bacteriologists have noted that media become more acid on sterilization. The difficulties in ensuring that a medium shall have a definite hydrogen ion concentration after sterilization are great. This difficulty is increased when, as is often the case, the medium contains glucose or lactose, and when the medium is sterilized in tubes.

If an excess of alkali be added to a medium containing glucose or lactose, it is rare that the reaction of the medium is above neutrality after sterilization. More often the hydrogen ion concentration rises to $P_H = 6{\cdot}0$. The attempt to compensate for this by adding an excess of alkali before sterilization is ineffective, because, owing to the increase of hydroxyl ions, the acid products are produced in greater quantity from the sugar. The products formed by the action of alkalies on sugars are many, and the acids which may be formed vary from saccharic acid to lactic acid. Another feature of the action of sugars in media containing amino acids is that these two combine to form so-called humin substances. To this is due the darkening on sterilization of peptone solutions containing glucose. One never obtains a sterile glucose peptone so light in tint as a plain broth containing no carbohydrate.

The only certain method of obtaining a glucose or lactose medium with a P_H greater than 7·0 is to add sterile sugar solution after sterilization of the nitrogenous part of the medium.

In this way the technical difficulties of preparing carbohydrate containing media of a P_H greater than 7·0 are increased. With

careful asepsis in a still room sterile sugar solutions may be added to broth with the loss of comparatively few tubes. The methods for doing so are given in any text-book on bacteriology.

Reaction of Solid Media.

Gelatine. The reaction of media containing gelatine may be easily determined if the medium is liquefied at 30° C. As a rule, gelatine is distinctly acid in reaction, and its addition to broth causes a rise in the hydrogen ion concentration of the mixture.

Agar. The addition of a good quality agar to broth has but little effect on the latter. The reaction of the medium may be estimated in the liquefied medium, but the temperature at which this is done makes the determination difficult. It is therefore better to use a clean agar which, preferably, has been washed, and take the reaction of the broth as that of the complete medium.

The reaction of the finished medium may be checked by adding the indicator to the liquefied medium, mixing it well and allowing it to cool thoroughly. The colours may then be compared, using the same precautions as in the case of broth.

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INTRODUCTION

During the pandemic of influenza in 1918, of which two waves appeared in the spring and autumn respectively, the Committee were able to arrange, so far as war conditions allowed, that the researches into the disease undertaken by civilian workers should be brought into relation to work being done at the same time for the Navy, the Army, and for the Air Force, and for this they were greatly indebted to the courtesy and active encouragement of the Directors of those Medical Services. The free interchange of opinions and the correlation of work done in so many different directions, both at home and overseas, have greatly aided the efforts towards better knowledge of this destructive infection and its results.

The Committee are now further indebted to the Army Medical Service for the transmission to them of the several reports here presented and for permission to publish them. It is hoped that the results of parallel work done elsewhere may follow in due course; some of these are appearing already in various scientific journals, and others the Committee will hope to present at an early date.

Of the present report the greater part consists in descriptive accounts of the bacteriology and pathology of the epidemic disease as observed among the Forces in France, and these records when collated with others are likely to have increasing value as our present imperfect knowledge of the true nature of the infective process increases, and gives the clue to the proper interpretation of the recorded external phenomena.

In the first part of the report are given the results of an inquiry by a group of workers at Abbeville, organized by Colonel S. L. Cummins, C.B., C.M.G., Adviser in Pathology to the British Armies in France, the members of which undertook, in addition to the descriptive study of the disease, an experimental investigation of its causation. The Committee are specially indebted to Colonel Cummins not only for allowing them to be kept in touch with the progress of the work, and for the introductory account of it he has written here, but also for the editorial supervision of this report in its various parts.

The work at Abbeville, which suggests that the primary infective agent in influenza is a filter-passing virus, distinct from the *Bacillus influenzae*, was unfortunately interrupted at too early a stage. Major H. G. Gibson, R.A.M.C., who was leader of the investigating team, succumbed himself to the disease when gravely overworked not only by his labours during the epidemic, but by unremitting and distinguished service given throughout the war. After the Armistice, moreover, military exigencies soon led to the stoppage of work in the Abbeville laboratories. The results of the

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work done up to that point, however, of which a preliminary account was given in the *British Medical Journal* of December 14, 1918, are here presented by Major Gibson's colleagues. As is well known, similar results as to the experimental transmission of the disease in animals by a filter-passing virus were being obtained quite independently at the same time by workers in another Army laboratory at Etaples, and these have been recently published.[1] It is plainly of the first importance that both sets of inquiries should be repeated by other hands, and that confirmation of their findings should be sought in every direction.

[1] Bradford, Wilson, and Bashford, *Quarterly Journal of Experimental Medicine*, 1919, 12, 259.

Medical Research Committee,
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June 30, 1919.

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INTRODUCTION.

By Colonel S. L. CUMMINS, C.M.G., A.M.S.

On the reappearance of influenza in epidemic form in October 1918, the officers-in-charge of laboratories throughout the British Expeditionary Force in France were encouraged to pay the closest attention to the disease and to report all findings of interest.

At the same time a ' Research Team ' was organized at Abbeville in order that bacteriologists, pathologists, and clinicians might co-operate in the investigation of the epidemic. The bacteriological and pathological work was entrusted to Major H. Graeme Gibson, R.A.M.C. (secretary to the Research Team), Major F. B. Bowman, C.A.M.C., Captain A. T. Nankivell, R.A.M.C., and Captain J. I. Connor, A.A.M.C. Captain A. T. Nankivell was moved to another station in December 1918, after which Captain J. I. Connor took sole charge of the work on morbid histology. The clinical work was entrusted to Major C. E. Sundell, R.A.M.C., officer-in-charge of the medical division of No. 2 Stationary Hospital. He was assisted, during some weeks, by Captain G. E. Beaumont, R.A.M.C., who, however, had to be transferred elsewhere in the course of military duty before the work was completed.

The research work on the rôle of a filtrable virus in influenza was rendered possible by the generous help of the Medical Research Committee. The provision of monkeys was a matter of no small difficulty, but these were promptly obtained and dispatched to France without delay through the kindness of the secretary, Sir Walter Fletcher, K.B.E., F.R.S., who was, at all times, ready to

further the research by every means in his power. Major-General Sir John Rose Bradford, K.C.M.G., C.B., F.R.S., the consultant physician to the Abbeville Area, kindly attended some of the meetings of the 'Research Team', and his assistance and advice were always at the disposal of the clinicians taking part in the work.

The work of the officers-in-charge of laboratories throughout the B.E.F. was beyond praise, and many reports of high value were received. It is regretted that considerations of space impose limits on the number of these reports which it is possible to publish at the present time, but they constitute a collection of records which will be of permanent value for army reference.

The present report is divided into two parts.

Part I consists of the work contributed by the Research Team, together with diagrams, photographs, and coloured illustrations, the latter by Sergeant A. K. Maxwell, R.A.M.C., whose services were kindly lent for the purpose by the Medical Research Committee.

Part II includes clinical, pathological, bacteriological, and serological reports from No. 3 Canadian General Hospital, No. 5 General Hospital, No. 25 Stationary Hospital, and from the Central Mortuary, Etaples Base.

In addition to the reports included in Part II, papers of the highest interest were also received from Major W. James Wilson, R.A.M.C., of No. 54 General Hospital, Captain C. Ponder, R.A.M.C., of No. 1 Stationary Hospital, Lieutenant B. A. I. Peters, R.A.M.C., of No. 14 General Hospital, Captains G. Bradbury and E. B. Krumbhaar, Medical Corps, U.S. Army, of No. 16 (Philadelphia, U.S.A.) General Hospital, and from Captain H. M. Perry, R.A.M.C., of No. 14 Stationary Hospital. Many valuable notes also reached me in private letters from Lieutenant-Colonel C. J. Martin, C.M.G., F.R.S., Major J. W. McNee, D.S.O., Captain A. Stokes, D.S.O., Captain J. Cruickshank, R.A.M.C., Major A. W. M. Ellis, C.A.M.C., and others.

The perusal of these reports and communications, as well as frequent visits to the laboratories in the B.E.F., has given me an exceptional opportunity of keeping in touch with the investigations undertaken in France, and this must be my excuse for attempting to summarize the impressions gained from a centralized study of reports from a large number of independent workers.

I. Identity of Summer and Autumn Epidemics. Epidemiological Notes.

In the *B. M. J.* of November 23, 1918, Captain M. Greenwood, R.A.M.C., sets out in a striking manner the characters of the curves of incidence in past influenza epidemics. In this paper it is stated that 'the fundamental characteristics of a primary epidemic of influenza are a very high attack rate and an approximately symmetrical distribution in time': ... 'the graph of the epidemic is an almost symmetrical curve; the fatality is low, rarely more than 1 per cent. of the cases.' 'A secondary epidemic affects a relatively small proportion of the population, is slower in reaching its maximum, and, thereafter, declines slowly and irregularly—more slowly than it increases; its distribution is asymmetrical, and there is less con-

centration around the maximum. Further, a secondary epidemic is characterized by a vastly higher fatality than a primary epidemic.'

Through the kindness of the D.G.M.S., British Armies in France, and of Captain A. H. Greg, O.B.E., R.A.M.C., statistical officer at the head-quarters of the D.M.S., L. of C., B.E.F., I have been enabled to prepare charts of incidence of the summer and autumn epidemics as they affected the British Expeditionary Force. As in Captain M. Greenwood's curves, the abscissae are weeks, the ordinates, expressed in terms of the number of cases recorded in the worst week, show the incidence on the British armies in France. In the absence of accurate figures as to the case mortality in the summer epidemic, I have charted the total mortality per month, from all diseases, throughout the year. This brings out clearly the very slight effect of the summer epidemic upon the mortality from disease, while the marked and terrible influence of the autumn epidemic is well seen.

The actual number of cases and, in the autumn epidemic, the case mortality, are shown in Tables I and II. It should be noted that, on the first appearance of the disease in May and June, many physicians preferred to use the non-committal description ' Pyrexia of Uncertain Origin ' (P.U.O.) rather than the diagnosis ' Influenza '. Table I therefore includes the cases admitted to hospital under both headings.

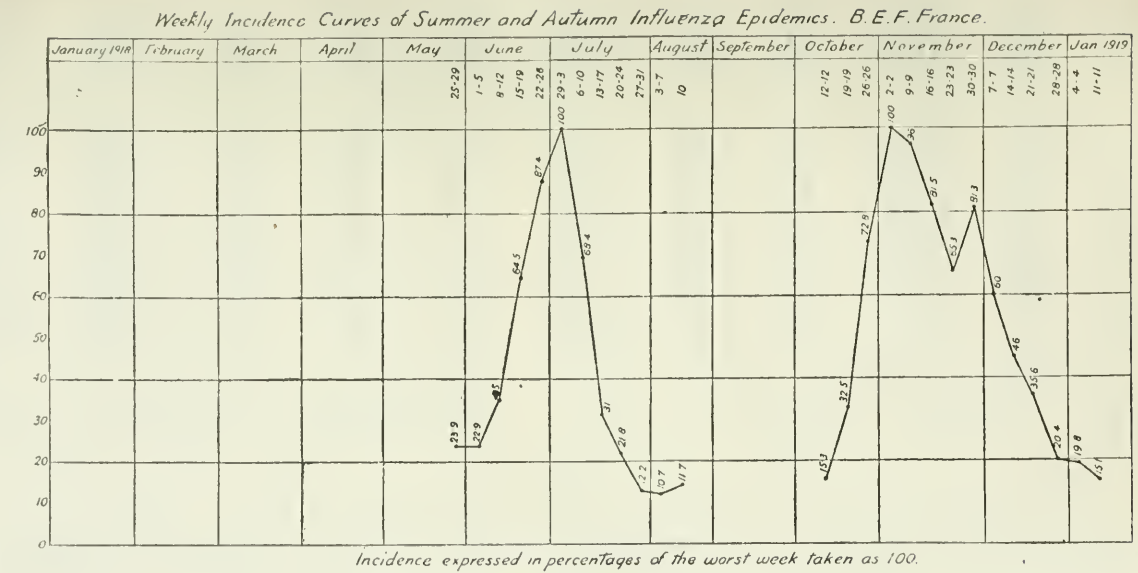
In the autumn epidemic many cases were diagnosed ' Broncho-pneumonia ' owing to the onset of this complication during the attack. The incidence under both headings is seen in Table II, but the totals have been used in compiling Chart I.

From these tables and charts it will be at once apparent that the summer and autumn epidemics exhibited, in every particular, the characters cited by Captain M. Greenwood as typical of a primary and a secondary epidemic of influenza respectively.

There can be no doubt that the two epidemics were identical in nature. The difference observed between the cases admitted in the summer and those seen in the autumn were differences in degree and depended on the enormously increased virulence of the infective agent in the secondary wave.

II. Immunity from previous Attacks.

A question of great interest is whether those attacked during the summer outbreak retained any appreciable immunity in the autumn. No conclusive figures could be collected on this point owing to the errors necessarily introduced by the unequal proportion of replacements of personnel in units and formations during the intervening months. Some units, engaged in the severe fighting of the late summer and autumn, must have changed their whole personnel during the period under review, while others, such as L. of C. units, probably underwent but little change. The question of diagnosis also introduces difficulty, as common colds and slight attacks of simple pyrexia tend to be called influenza during epidemics of this disease, and it is by no means certain that a patient stating that he had had a previous attack had really suffered from the disease.



Incidence expressed in percentages of the worst week taken as 100.

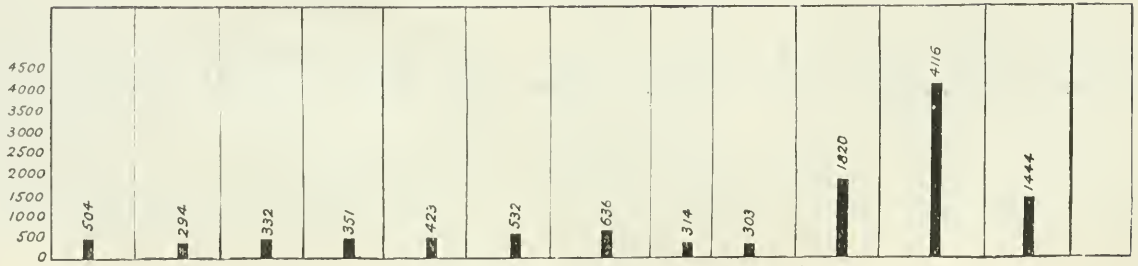


CHART I.

Table I.

Weekly Admissions.

Epidemic of Influenza (including Cases diagnosed P.U.O.). From Week ending May 25, 1918, to Week ending August 10, 1918.

B.E.F., FRANCE.

Week ending.	25.5.18.	1.6.18.	8.6.18.	15.6.18	22.6.18.	29.6.18.	6.7.18.	13.7.18.	20.7.18.	27.7.18.	3.8.18.	10.8.18.	*Total.*
	11,001	10,624	16,186	29,880	40,471	46,275	31,693	14,344	10,086	5,675	4,966	5,414	226,615

Table II.

Epidemic of Influenza (including Cases diagnosed Broncho-pneumonia). Total Admissions and Deaths. From Week ending October 12, 1918, to Week ending January 18, 1919.

B.E.F., FRANCE.

Week ending	*Influenza.*		*Broncho-pneumonia.*		*Total.*		*Week's case mortality.*	*Totals to date.*		*Case mortality to date.*
	New cases.	*Deaths.*	*New cases.*	*Deaths.*	*New cases.*	*Deaths.*		*New cases.*	*Deaths.*	
1918										
Oct. 12	1,665	1	225	41	1,890	42	2·2	1,890	42	2·2
Oct. 19	3,636	19	384	105	4,020	124	3·1	5,910	166	2·8
Oct. 26	8,287	93	693	258	8,980	351	3·9	14,890	517	3·5
Nov. 2	11,306	308	1,029	457	12,335	765	6·2	27,225	1,282	4·7
Nov. 9	10,846	507	1,006	484	11,852	991	8·4	39,077	2,273	5·8
Nov. 16	9,407	421	748	412	10,155	833	8·2	49,232	3,106	6·3
Nov. 23	7,339	337	720	344	8,059	681	8·5	57,291	3,787	6·6
Nov. 30	9,400	327	634	274	10,034	601	6·0	67,325	4,388	6·5
Dec. 7	6,920	248	485	222	7,405	470	6·3	74,730	4,858	6·5
Dec. 14	5,308	136	363	129	5,671	265	4·7	80,401	5,123	6·4
Dec. 21	4,178	81	219	78	4,397	159	3·6	84,798	5,282	6·2
Dec. 28	2,404	48	121	47	2,525	95	3·8	87,323	5,377	6·2
1919										
Jan. 4	2,348	28	100	28	2,448	56	2·3	89,771	5,433	6·1
Jan. 11	1,767	30	97	40	1,864	70	3·8	91,635	5,503	6·0
Jan. 18	1,925	29	110	23	2,035	52	2·6	93,670	5,555	5·9

From records at my disposal it would seem that out of 965 patients of the autumn outbreak questioned as to a previous attack, only 248, or about 26 per cent., stated that they had had influenza during the summer ; and a considerable number of these had had the disease so mildly that they were not sent to hospital. It is definitely stated by Major J. W. McNee, D.S.O., that, out of 500 patients questioned, only 20 per cent. had suffered from influenza in the summer. The severe cases, without exception, stated that they had had no previous attack. Allowing a margin for errors of diagnosis, these figures appear to suggest that some degree of immunity had been acquired. The following quotation from a letter received from Lieutenant-Colonel Elser, Medical Corps, U.S. Army, points in the same direction:

' In July about 80 per cent. of the Command at one of the Base hospitals (numbering approximately 228) suffered from " 3-day fever ", while in this present epidemic very few cases developed in this Command, and those almost invariably among individuals who had joined this organization recently.'

It cannot be claimed that these records are final or conclusive, but they point, with considerable weight, to the production of some amount of immunity. This is what might be expected, as it is difficult to believe that an epidemic can owe its cessation entirely to a diminution of virulence of the causative agent, and it is, on the whole, more simple to explain the cessation of an outbreak in terms of the production of a relative immunity in the population concerned.

III. Frequency of Haemorrhage.

Nothing is more striking than the unanimity with which all observers mention haemorrhage as a prominent feature of the disease in the autumn epidemic. This point is hardly mentioned in reports received during the summer, but records of the more severe cases show, nevertheless, that a tendency to haemorrhage existed then as later. In the post-mortem notes included in the Report by the Committee of the Director-General's Advisory Council (*B. M. J.*, November 9, 1918), it is stated that ' sub-pleural and interstitial haemorrhages were seen in 18 cases (out of 39 examined), but only as small localized areas '. Other post-mortem records of the same period afford similar information.

In reports on the autumn outbreak, on the contrary, constant reference is made to haemorrhage, blood being noted in the sputum and faeces, and epistaxis being often recorded. Notes kindly furnished by Dr. L. Stewart Sandiman, Chief Medical Superintendent, Q.M.A.A.C., show that menstruation is very frequently precipitated by attacks of influenza. The report by Captain T. H. G. Shore, R.A.M.C., lays much stress upon the constancy with which haemorrhages were noted *post mortem* and suggests their importance as a factor in the inception of the pulmonary complications of the disease. The numerous pathologists who have sent in reports are almost unanimous in noting haemorrhages in the lungs, and mention is made of bleeding in the suprarenals, the brain, the pericardium, the pleura, and other situations. Haemorrhage in the rectus muscle is frequently reported. An interesting note by Captain Murray

Lyon, R.A.M.C., records haemorrhages in the rectus muscle in 20 per cent. of 100 cases examined, and Major W. J. Wilson, R.A.M.C., describes the presence of Zenker's degeneration in the fibres of the rectus muscle in 32 out of 92 cases investigated. In 11 of these cases there was haemorrhage amongst the degenerated muscle fibres.

The haemorrhages are obviously much more common in situations, such as the lungs and rectus muscle, that are subject to strain during violent respiratory effort, as in coughing. Coughing is often continuous and trying in influenza cases, owing, perhaps, to the tracheitis so commonly found or to the irritation of enlarged and congested lymphatic glands in the neighbourhood of the trachea and bronchi. That the strain resulting from this coughing is severe is proved by the fact that emphysema is often found *post mortem* in the anterior mediastinum, and that, as in gas poisoning, air sometimes finds its way up into the tissues of the neck. It is not to be wondered at that, where toxic degeneration of muscle fibres or other tissues is so frequent, vessels often rupture under the strain of respiratory effort, or indeed without this strain where the degeneration is intense.

Stress is laid on this tendency to haemorrhage because it links up the lesions following animal inoculations with ' filtrates ' or with ' Noguchi ' cultures with those found in human cases.

A reference to the post-mortem findings in the monkeys and other animals investigated by Major H. G. Gibson, Major F. B. Bowman, and Captain J. I. Connor, shows that the production of haemorrhagic oedema is a constant occurrence. In these animals, killed at selected dates after inoculation, the lung haemorrhages form the essential pathological lesion. A striking link between the findings in infected animals and human cases is afforded by a post-mortem record of an early case in the paper by Patterson, Little, and Williams : ' In one case, whose bronchitic signs dated from only two days before death, only one small area of bright red consolidation near the hilus of the left lower lobe was found, in addition to a tremendous haemorrhagic engorgement of the whole of the lungs.'

The period of the case at which these haemorrhages occur seems to coincide with the moment of maximum ictus of the infection. It may be assumed that the causative organism cannot always or at once establish itself in complete ascendancy in the tissues of the infected person. The severity of the case will depend on whether, to what extent, and how rapidly, the virus gains the upper hand.

The tendency to haemorrhage may be taken as a rough measure of the virulence of the epidemic. Where the cases are mild, as in the summer of 1918, haemorrhages are very rare ; where severe, as in the autumn, they form the outstanding feature of the disease. It is probable that many lung haemorrhages of slight degree may be absorbed without untoward results. In monkeys, in the absence of secondary bacterial infections, fairly extensive lung haemorrhages can exist without apparent inconvenience to the animal. We know, from the study of cases of gas poisoning, how rapidly the lung can free itself from effused fluids provided that no undue strain on the respiratory mechanism leads to the inception of the vicious circle of excessive oxygen-want and consequent excessive respiratory effort. It may be assumed that many cases of influenza, clinically mild, yet

suffer from pulmonary lesions that only require a secondary bacterial infection to convert them into grave broncho-pneumonia. It appears worth while to lay great stress on this point. Even the mildest case of influenza may become grave if too early exertion or any other cause is permitted to disturb the physiological balance and thus render possible the invasion of the injured tissues by the bacteria of the respiratory tract.

IV. Morbid Anatomy and Histology.

These subjects are so thoroughly dealt with in the appended reports that very little remains to be said. An interesting suggestion by Captain A. T. Nankivell may perhaps afford an explanation of the formation of the haemorrhagic areas seen in the lungs in cases dying early in the disease and in experimental animals. Captain Nankivell thinks that these appearances may be explained 'by the occurrence of haemorrhage in some relatively distant bronchus or bronchiole, the blood flowing down, or being inspired, into healthy lung tissue, filling the majority of the alveoli there, but, owing to clotting or some mechanical factor, not penetrating into every alveolus'.

Such a haemorrhagic area of lung tissue would be liable to invasion by bacteria through the injured bronchial walls. In this connexion it is interesting to recall that practically all the secondary bacterial contaminations of influenzal lungs are organisms that grow best on media containing blood in some form.

The conclusion of Tytler, Janes, and Dobbin is that 'the interstitial broncho-pneumonia is, both from gross and microscopical examination, evidently an extension of infection through the bronchial wall to the surrounding lung tissue; not an infection of the alveoli by way of the natural passages'.

These two quotations appear to present a reasonable explanation of the early and the late phases of the lung complications in influenza.

Once started, the secondary bacterial infections may proceed throughout the injured and water-logged tissues with such unrestrained violence that the whole lung is found literally permeated by bacteria so that every alveolus is packed with them. Sections of lung from the more severe cases, appropriately stained, give a terribly clear idea of the helplessness of injured human tissues in the face of bacterial invasion.

Attention is directed to the valuable observations of Captain T. H. G. Shore, R.A.M.C., on the condition of the heart in post-mortem examinations of influenzal patients. His conclusion, that 'it would be curious if such hearts could sustain a normal intra-ventricular pressure', forms an interesting commentary on the clinical picture in these cases.

V. Bacteriology.

A. *A Filter-passer as the Primary Causative Agent.*

The question of supreme importance is whether, in view of recent observations, the causative agent of influenza is or is not a filter-

passing organism. Investigations by C. Nicolle and Lebailly and others have pointed strongly to the conclusion that the disease may be reproduced by inoculation of filtered bronchial secretions from human cases. Major H. G. Gibson, Major F. B. Bowman, and Captain J. I. Connor, working at Abbeville, have obtained results confirming and amplifying those of C. Nicolle and Lebailly in the infection of monkeys and other animals by these filtrates. This investigation, published in the *British Medical Journal* of December 14, 1918, formed, it is believed, the first British contribution to the problem of a filtrable virus in Influenza. Further, applying the Noguchi technique in the manner employed by G. Foster in the case of common colds, they have been able to obtain a growth of very minute anaerobic Gram-positive globoid bodies, both from filtrates and from organs of infected animals, and, on injecting these cultures into monkeys, rabbits, and guinea-pigs, have reproduced the haemorrhagic pulmonary lesions now coming to be regarded as characteristic of the disease in animals.

The cultural work of these observers affords independent confirmation to that carried out a few months earlier by Captain J. A. Wilson at Etaples (Bradford, Bashford, and Wilson, *B. M. J.*, February 1, 1919). Major Gibson, Major Bowman, and Captain Connor were unaware of Captain Wilson's work which, owing to its forming part of a larger research, was not at once made public, and their cultures were obtained with a modification of the Noguchi technique differing in certain particulars from that employed at Etaples.

That two series of observations, carried out independently, should thus confirm each other, greatly strengthens the case for the new organism. It is necessary, however, to preserve a critical attitude until the question has been more thoroughly investigated. ' Passage work ' has been, so far, practically limited to animals owing to the danger of using human volunteers and to the fallacies incident to human ' passage ' experiments during a pandemic. It is not always safe to regard the results of animal experiments as applicable to man. There are many difficulties to be overcome in working with so-called ' filter-passing ' organisms, or indeed with any organisms of very minute size, and these difficulties and limitations must be taken into account in considering the work now brought forward.

An obvious criticism is that whereas the incubation period of influenza is known to be definitely in the vicinity of forty-eight hours, the animals infected by Nicolle and Lebailly and by Gibson, Bowman, and Connor did not show signs of illness before the sixth or seventh day. This objection can be parried theoretically in several ways, but it must be admitted that controversy on the point is still in the realm of theory and that further knowledge can only be gained by continued experimental work.

All that can now be stated is that a very good case has been made out for a ' filter-passer ' as the causative agent in influenza, and that, if the haemorrhagic lung oedema produced by inoculation of animals be accepted as identical with human influenza, Koch's postulates can be said to have been fulfilled.

B. *Other Organisms as Secondary Infective Agents.*

(a) *B. influenzae (Pfeiffer).* Had it not been for these recent observations which have gone so far towards demonstrating the etiological rôle of a filter-passing organism, the evidence in favour of *B. influenzae* would probably have been regarded as conclusive. As it is, this bacillus must still be admitted to be the earliest and most constant 'associate', appearing on the scene within the first hours of the attack. To what extent it facilitates the operations of other and more virulent germs still remains to be discovered.

Tytler, Janes, and Dobbin, in commenting on their finding of *B. influenzae* in 90 per cent. of the cases examined, sum up as follows: 'Allowing for errors of technique, unavoidable in a series of this size . . . this means that the bacillus was constantly present.'

The presence of *B. influenzae* in a high proportion of cases within the first week of the disease, and at a time when streptococci and pneumococci were much less frequently found, is well shown in the chart in the paper by Patterson, Little, and Williams. These observers cultivated *B. influenzae* from sixty-two out of sixty-three fatal cases.

Not only is *B. influenzae* present in nearly every case but it tends to evoke immune responses early in the disease.

In confirmation of the work of Captain J. Cruickshank in the summer outbreak, the presence of specific agglutinins for this organism has been demonstrated, during the autumn epidemic, by Captain A. Fleming, Captain H. H. Perry, Major H. G. Gibson, Major F. B. Bowman, and by Captain P. Hartley whose report on this subject is included in Part II; but the reaction has not yet been shown to be either so constant or so clear-cut as to serve as a reliable diagnostic method. Its interest lies, rather, in the evidence which it affords of the early presence of *B. Pfeiffer* as an organism actually evoking immunizing responses in the cases examined. It is worthy of remark that the agglutination was most complete and most constant in blood-samples collected up to and including the seventh day, after which the phenomenon was less frequently demonstrated.

B. influenzae has been cultivated from the blood stream on several occasions, though this is rare during the normal course of the disease. That it invades the circulation fairly frequently, as a terminal infection, is shown by the observations of Lieutenant B. A. I. Peters, R.A.M.C., who recovered it from the heart's blood in nine out of forty-one cases examined by him *post mortem*.

At the same time nothing is more curious, in view of the constant presence of *B. Pfeiffer* in influenza cases in France and elsewhere, than the negative reports by workers of undoubted merit in certain other localities. In the *Medical Supplement of the Daily Review of the Foreign Press* of September 1, 1918, negative or inconclusive findings of the *B. influenzae* are recorded by Gruber, Friedmann, Uhlenhuth, Kolle, and even Pfeiffer himself.

The technique for the isolation of *B. influenzae* has been much improved of recent months, and it becomes a question of interest as to how frequently this organism will be found present in the sputum of chest cases other than influenza during times when this

disease is not epidemic. Figures kindly given me by Colonel J. F. Siler, Medical Corps, U.S. Army, Director of Laboratories, American Expeditionary Force, show that out of 2,179 healthy persons serving in medical units, 595, or nearly 27 per cent., were found to be healthy ' carriers ' of *B. influenzae* at a time when the disease was prevalent ; a percentage not very much below that found in early cases of influenza examined by throat-swabbing before sputum is available. It is possible that *B. influenzae* may be much more common than was supposed in the normal respiratory tract.

(b) *Other Organisms.* The papers included in this report give a clear picture of the general prevalence of other organisms as secondary infective agents in influenza in France. Streptococci, pneumococci, staphylococci, and meningococci are the more important organisms found. These, with the exception of the pneumococci, seldom give rise to septicaemic infections except in fatal cases shortly before death ; but the conditions prevailing in influenzal lungs greatly favour their activity, and the principal danger to influenzal cases appears to be the tendency to secondary infections of the damaged pulmonary tissues.

It would seem that the secondary bacteriological findings conform to the varying flora of the human respiratory tract in different localities, the contradictory nature of some of the reports depending upon this factor ; thus haemolytic streptococci may be found as the commonest organisms in one place while they are replaced almost entirely by *Streptococcus viridans* in another. Much confusion has undoubtedly arisen in differentiating pneumococci from some of the capsulated and lanceolate streptococci, but there seems no doubt that the proportion of positive findings of true pneumococci varies greatly in different localities.

The paper by Captains A. V. Bock and J. L. Stoddard of the Medical Corps, U.S. Army, recording their findings in a series of cases of which 64 per cent. were Americans, will be read with interest in this connexion and should be compared with the findings of Tytler, Janes, and Dobbin, at No. 3 Canadian General Hospital, where lobar pneumonia was hardly ever observed.

The tendency for the pneumococcus to gain entrance to the blood stream is well brought out in this paper and is confirmed by the isolation of this organism in blood cultures in twelve out of forty-four cases by Dr. Little and Miss Williams.

Major Tytler calls attention to the very high percentage of staphylococcal infections, and this is confirmed by a report by Major W. J. Wilson on cases examined in the same area. Similar findings are reported from Malta by Captain Adam Patrick (*The Lancet*, January 25, 1919). On the other hand, staphylococci do not take a prominent place amongst the organisms isolated from the cases, mostly German prisoners of war, investigated by the Abbeville Research Team.

With all these variations in the bacteria of secondary infections, the morbid anatomy and morbid histology remain wonderfully constant, the differences representing stages in a progressive process rather than true variations of type. Except for the fact that the rare cases of lobar pneumonia are usually found to be associated with true pneumococci, the variations in morbid anatomy appear

but little connected with variations in the associated bacteria. To quote from the paper by Tytler, Janes, and Dobbin :

' An analysis of the relation of the type of organism isolated to the type of lesion present does not reveal any features striking enough to definitely ascribe any type of lesion to infection with any one particular organism.'

An important factor underlying the production of secondary lung complications would appear to be the degree of injury to pulmonary tissues by the primary etiological agent of the disease. The resulting areas of haemorrhagic oedema afford a ready portal of entry and ideal conditions of growth for the organisms already existing upon the surface of the respiratory tract.

The whole clinical and pathological picture becomes intelligible if we can postulate a primary etiological agent acting locally upon the respiratory surfaces and generally through its toxic products in such a manner as to prepare the way for invasion by the prevailing respiratory flora. The work of Gibson, Bowman, and Connor at Abbeville and of Wilson at Etaples holds out a promise that this explanatory link may now be supplied.

PART I

I. THE ETIOLOGY OF INFLUENZA: A FILTRABLE VIRUS AS THE CAUSE

WITH SOME NOTES ON THE CULTURE OF THE VIRUS BY THE METHOD OF NOGUCHI

BY

Major H. Graeme Gibson, R.A.M.C.,
Major F. B. Bowman, C.A.M.C.,
AND
Captain J. I. Connor, A.A.M.C.

Since the results of our preliminary experiments were reported in the *British Medical Journal* of December 14, 1918,[1] in an article entitled ' A Filtrable Virus as the Cause of the Early Stage of the Present Epidemic of Influenza ', further work has been carried out which confirms that already reported.

We have also attempted to cultivate the ' filtrable virus ' of influenza and have made experiments in the transmission of the disease to animals by inoculation with the cultures so obtained.

These cultural experiments were suggested by one of us (H. G. G.) at an early stage of the work, and later, a paper by G. Foster,[2] to which we had access, clearly showed that this part of the work might prove to be a very important part of the investigation.

The animals used by us for experimental purposes have been baboons, *Macacus rhesus* monkeys, rabbits, guinea-pigs, and mice. By the inoculation of sputum, both filtered and unfiltered, from cases of influenza, we have succeeded in producing, in all these animals, lesions that appear similar to those seen in human cases of the disease.

For experiments with blood transmission we used *M. rhesus* monkeys and mice. Although the results obtained in the only two cases in which monkeys were inoculated with blood were not wholly satisfactory, the experiments with mice gave a high percentage of positive results and it seems to be possible to transmit the virus by means of infected blood to the latter animals. It should be noted that the mice received a very much larger dose per body weight than the monkeys and this factor, no doubt, played a part in the results obtained.

With cultures it was found to be possible to infect baboons, monkeys, rabbits, guinea-pigs, and mice. Owing to the grave nature of the influenza epidemic in progress, it was not thought advisable to attempt any experiments in the transmission of the disease to human volunteers, both on account of the danger involved and owing to the fact that there would have been no guarantee, in the face of so

widely-spread an epidemic, that the individual to be experimented upon had not already been exposed to infection.

Before going on to report the results obtained it seems desirable to describe, in some detail, the technique employed by us in our investigations.

I. Housing of Animals.

A. *Monkeys.*

The monkeys were kept for at least a week after their arrival before being used for any experimental purpose, in order that they might become accustomed to their new surroundings and that we might be sure that they were in good health. The advisability of this course was borne out by the fact that two of our monkeys developed other diseases while under observation, one dying two days after arrival from pneumonia associated with M'Gowan's bacillus of distemper and to which reference is made later, and the other from tuberculosis.

The monkeys, from the time that they arrived, were kept in separate cages. These cages were maintained in clean condition by washing out with cresol solution. The cages were separated from each other by means of wooden partitions and the whole house in which the monkeys was kept were warmed by means of a stove.

B. *Rabbits, Guinea-pigs, and Mice.*

Until used for experimental purposes, all the rabbits were kept together and the same applies to the guinea-pigs and mice. After an animal had been inoculated it was kept in a cage by itself and rigorously segregated from the remainder.

No cage used for the purpose of housing any animal, whether inoculated or not, was used for fresh animals until it had been thoroughly disinfected.

II. Preparation of Material used for Inoculation.

A. *Sputum.*

On the sputum being brought to the laboratory in clean sputum pots, a portion was examined by means of a direct smear and by culture. The cultures were made on defibrinated human blood agar and in glucose serum broth. From various samples of the sputum used, pneumococci, streptococci of the haemolytic and *viridans* groups, *M. catarrhalis,* staphylococci and *B. influenzae* (Pfeiffer) were isolated.

The remainder of the sputum was then taken and ten times its volume of normal saline was added to it. This was placed in a sterile milk bottle with a clamp stopper, which contained sterile glass beads, and it was then vigorously shaken by hand for five minutes. The contents of the bottle were then centrifuged for one minute and a half at from 1,500 to 2,000 revolutions per minute, after which the supernatant fluid was decanted into a sterile flask.

At this stage the mixture was either used for inoculation in its unfiltered state, in which case a culture was first taken from it,

or was filtered through a Chamberland L. 1 bis or Chamberland F. filter under a negative pressure of 50 cm. of mercury. The filtrate was then tested for sterility, using the same media as mentioned above for culturing the sputum. In no case was any growth of non-filtrable organisms obtained. The filtrate obtained was used for inoculation, except on two occasions, when a portion of the filtrate was first heated in a water bath at 71° C. for half an hour and was then inoculated subcutaneously into mice.

B. *Blood.*

In the case of blood the technique employed was slightly different, The blood was drawn off from the median basilic vein by a syringe with the usual aseptic precautions.

In the majority of cases the animals to be inoculated were taken into the ward in which the patient suffering from influenza was in bed. Usually about 10 c.c. of blood were drawn off, a few drops were sown into a defibrinated-blood agar plate and 3 c.c. inoculated into mice which were the animals chiefly used for these experiments.

In one instance, where an attempt to infect monkeys was to be made with unfiltered and filtered blood, 20 c.c. were drawn off by means of a needle and sterile rubber tubing which led into a flask containing 2 c.c. of 10 per cent. sodium citrate. Cultures were taken from this and proved sterile. The remainder was divided into two parts, A and B.

Of these two parts, 10 c.c. of A were placed in a sterile measuring cylinder and 40 c.c. of sterile distilled water were added to lake the blood. This was cultured and proved sterile for non-filtrable organisms. The laked blood was then filtered through a Chamberland L. 1 bis filter and the filtrate similarly tested and proved free from non-filtrable germs. This was again divided into two parts, one of which was left unheated and the other heated to 55° C. for half an hour in a water bath.

In the meanwhile, the part B mentioned above and which consisted of 10 c.c. had been left standing at room temperature during the process of preparing part A, in order that the whole blood might have been kept for a similar period outside the body before inoculating it into monkeys. This period was one of about two and a half hours.

III. A General Picture of the Clinical and Pathological Results Obtained in Animals Inoculated with the Virus in those Instances in which a Positive Finding was Recorded.

The clinical and pathological picture obtained was the same, whether unfiltered or filtered influenzal sputum was used as the infecting agent.

A. *Clinical.*

This varied somewhat with the kind of animal employed. In monkeys a clinical picture of depression, anaemia, with a staring coat and in one instance diarrhoea was obtained, though this was by no means constant, and we were struck with the degree of damage

that might be present in the lungs without any marked clinical symptoms or signs that anything was amiss with the animal. *When symptoms were noticed, they appeared on the fifth to seventh day after inoculation.*

The temperature charts of the monkeys gave us very little clue as to what one might expect to find *post mortem* after the animal was killed. The temperatures of the monkeys were taken twice daily from the time we received them. The average temperature seemed to be about 102° F., but the range of temperature obtained with normal monkeys was never noteworthy, temperatures of anything between 99·6° F.–104° F. being recorded. After inoculation there was never any marked rise in temperature, but we gained a general impression that the temperatures were inclined to swing more after this had taken place. The other animals, except mice, showed no marked symptoms.

One or two of the mice inoculated with the virus showed some sign of respiratory distress at varying intervals up to three days after the inoculation, but these subsequently recovered. Some of the mice died when a large dose was given and in only two cases was the death of the animals witnessed. In these two cases the mice were seen lying on their backs with obvious respiratory distress and clutching at the cork in their cage with their front legs. In all other cases of death in the experimental animals, they were found dead in their cages. In one instance two mice, previously infected with coccidiosis, died, while another mouse which was inoculated with the same filtrate and which had no other intercurrent affection showed no symptoms, although when killed its lungs presented the usual picture. In another case five out of six mice inoculated with large doses of blood from a case of influenza died within forty-eight hours. As a rule, we were struck by the paucity of the symptoms in animals inoculated with unfiltered or filtered sputum given in those cases which presented gross pathological lesions in the lungs after being killed.

B. *Pathological.*

The pathological lesions found in all animals in which positive results were obtained, whether they died or were killed, closely resembled each other and also the conditions found in man in cases which died at an early stage in the disease. The condition found was the same in the monkey, rabbit, guinea-pig, and mouse. For the purpose of this communication it is proposed to give a general description of the macroscopic and microscopic lesions observed.

(a) *Macroscopic appearances. Respiratory tract.* The larynx of the animal was generally normal, but in one or two instances there was some slight injection present.

The trachea was often red and congested, though this condition was not absolutely constant. A much more constant feature was the presence of frothy blood-stained fluid in the lower part of the trachea which oozed up from the bronchi. *The lungs* themselves in every case showed patches of a haemorrhagic nature of varying sizes. For the most part they were more marked on the posterior than on the anterior surfaces of the lungs.

These haemorrhagic areas were not only seen sub-pleurally, in which case they showed a tendency to spread into the lung substance to a slight extent, but, on section, they were also seen to be scattered through the lung substance itself, varying greatly in size, and in one or two cases the lung substance was of a dark red to purple colour and presented a wet appearance. In nearly all cases the lower lobes were the ones most affected. On cutting into the lung substance in several instances a viscid dark purple fluid dripped from the cut surface, closely resembling that seen in human cases of influenza. No evidence of broncho-pneumonia was seen in any animal lung examined by us.

Bronchial glands were found to be enlarged in some instances.

The liver was not markedly affected in the majority of the cases, though in a few there was a certain suggestion of yellowish mottling.

The other organs were apparently normal to the naked eye. The most marked changes were always found in the respiratory tract.

Pleural sacs. In the large majority of cases there was no evidence of any pleurisy, but in the case of one monkey, which was killed about three weeks after its inoculation with filtered sputum from a case of influenza, there were some adhesions present, apparently of between two and three weeks' standing. In the case of a monkey inoculated with unfiltered sputum there were some recent adhesions between the lower lobe of the lung and the diaphragm and between the lobes of the lung. In one mouse also the lungs on both sides were bound down to the parietal pleurae.

(b) *Microscopic appearances. Lungs.* Examination of over 200 sections. (See Plates VIII, IX, X.)

Microscopic examination of the lungs of affected animals presented a very similar picture to certain areas seen by us in some of the human lungs taken *post mortem* from men who had died at an early stage of the disease. Judging from the examination of mice dying at a very early stage, the first miscrocopic sign seems to be an acute dilatation of the capillaries in the alveolar walls, and some sections showed a certain amount of actual haemorrhage into the alveoli. In the most marked animal lungs there was an almost universal consolidation, the alveoli being filled with what appeared to be an inflammatory and haemorrhagic exudate.

The bronchi and larger vessels were often seen filled with the same exudate, and the impression was conveyed that the circulation in some areas had been stopped. The mucous membrane of the bronchi was usually intact and some cells showed a mucoid accumulation. Leucocytic accumulation was, as a rule, scanty, but some of the lungs taken from animals killed at a later date showed a certain amount of leucocytic infiltration, and in one monkey killed three weeks after inoculation there was some destruction of the lining membrance of the smaller bronchi.

In no instance was any approach to grey hepatization seen. The high power in some cases showed the exudate in the alveoli to consist of an amorphous material and in several instances the remnants of degenerate red-blood corpuscles were seen, some of which still maintained their original shape.

IV. Animal Inoculation and Cultural Experiments with Filtrable Virus.

The work may be divided into four parts :

A. Inoculation of animals with sputum from cases of influenza.
B. Inoculation of animals with blood from cases of influenza.
C. Passage of the virus from animal to animal.
D. Cultural experiments and inoculation of cultures into animals.

A. *Inoculation of animals with Sputum from Cases of Influenza.*

(a) *Source of infected material.* The sputum used was as a rule collected as early as possible in the disease. As uncomplicated cases of influenza as a rule present a pyrexial period of only a few days' duration we considered that it would be during those few days that we should have the greatest chance of recovering the virus. As a rule a certain amount of sputum was obtainable on the second or third day, and this, generally speaking, was frothy, of a greyish yellow colour, tenacious, often markedly bloodstained, and did not present the numular appearance seen in cases of bronchitis.

(b) *Method of inoculation and size of dose given. Sputum.* Emulsions of unfiltered and filtered sputum were inoculated by the same routes and the size of the dose was the same in each case. When dealing with monkeys the methods of administration of unfiltered sputum reported by Nicolle and Lebailly was followed.

This consisted in injecting 0·25 c.c. of the emulsion under the conjunctiva of each eye and instilling 0·5 c.c. of the emulsion up the animal's nose. In one instance we inoculated one monkey by the conjunctival route alone, and gave another monkey 0·5 c.c. of the same filtrate up its nostrils alone. The former gave a positive result while the latter proved negative.

Rabbits. These animals were given 1·2 c.c. of the filtered sputum either intravenously or subcutaneously. Positive results were obtained by both methods.

Guinea-pigs and Mice were always inoculated subcutaneously whether unfiltered or filtered sputum was used. Guinea-pigs were usually given 1 c.c. and mice, when used, received 0·25 c.c. of the unfiltered or filtered sputum.

In dealing with the results obtained it is convenient to separate the various animals employed into different groups, taking the monkeys first, we may divide them into two main groups according to whether the sputum used as the infecting agent was taken from the patient during the first three days of the disease or at a later date. The results are shown in the subjoined table :

Group I. Sputum collected early.

Type of Monkey.	*Material used for inoculation.*	*Date of disease on which sputum was taken.*	*Result.*
1. *M. rhesus*	Unfiltered sputum	3rd day	Positive
2. *M. rhesus*	,, ,,	3rd day	Doubtful
*3. *M. rhesus*	Filtered ,,	3rd day	Positive
*4. *M. rhesus*	,, ,,	3rd day	,,
*5. *M. rhesus*	,, ,,	2/3 day	,,
*6. *M. rhesus*	,, ,,	3rd day	,,
7. *M. rhesus*	,, ,,	3rd day	Negative

* See Plates III and IV, IX and X.

This gives 80·0 per cent. positive results among the *M. rhesus* monkeys inoculated with *filtered* sputum taken from cases of influenza before the end of the third day of the disease. Out of the two monkeys inoculated with *unfiltered* sputum taken during the same period one positive result was obtained and in the other instance although the macroscopic examination revealed little, the microscope showed patches of acute inflammation with the typical inflammatory exudate. Thus 85·7 per cent. of all monkeys inoculated with sputum filtered or otherwise gave positive results if the doubtful case is included; if excluded 71·4 per cent. were positive.

Where sputum taken at a later date was inoculated the results obtained were less satisfactory. One monkey was inoculated with *unfiltered* sputum taken on the sixth day from a case of influenza. A negative result was obtained. A monkey inoculated with the filtered sputum from the same case also showed no signs of disease *post mortem*. A monkey inoculated with filtered sputum from a case of influenza taken on the fifth day gave a positive result.

Group II. Sputum collected later.

Type of Monkey.	*Material used for inoculation.*	*Date of disease on which sputum was taken.*	*Result.*
1. *M. rhesus*	Unfiltered sputum	6th day	Negative
*2 *M. rhesus*	Filtered ,,	6th day	,,
3 *M. rhesus*	,, ,,	5th day	Positive

* See Plate VII A.

In this instance two out of three attempts failed, or only 33·3 per cent. were positive. These figures are very small and insufficient to justify any final opinion as to the period in which it may be impossible to obtain the virus from a case of influenza, but with the number of monkeys which we had it was thought more profitable to concentrate our attention on sputum obtained at an earlier date. The time up to which the virus can be recovered must form the basis for further work on this subject.

An attempt to infect a monkey with filtered sputum instilled up its nostrils without any subconjunctival injection failed, although subconjunctival injection, without nasal instillation, of the same filtrate, gave a positive result in another monkey.

Controls. Two monkeys were inoculated with filtered sputum obtained from two cases of acute bronchitis on the third day of the disease. The sputum was prepared and filtered in the same way and the monkeys were inoculated subconjunctivally and by nasal instillation in each case. They were given the same dose, but were both negative as regards symptoms and both macroscopic and microscopic examination of their lungs.

Another monkey died two days after arrival with a lobar pneumonia associated with M'Gowan's bacillus of Distemper. The post-mortem findings were totally different from those seen in our experimental animals. Microscopically there was no great engorgement of capillaries and no haemorrhagic exudate in the alveoli.

The obtaining or not of a positive result by means of the injection of monkeys with filtrable viruses depends very much more on the

dose given than in the case of experimental infections with non-filtrable germs. At present it is not possible to determine the dose that is being given. It is known that while these viruses, as a rule, reproduce the picture of the human disease, as, for instance, in the case of polyomyelitis, the certainty of producing a positive result is not nearly so great as when dealing with the non-filtrable bacteria which are pathogenic for animals. In view of these facts the animal experiments with monkeys appear to us to be quite significant as far as they go.

Rabbits. Four rabbits were inoculated. Of these, two were inoculated with filtered sputum taken on the third day from a case of influenza. One of these rabbits was given 1 c.c. of the filtrate intravenously and the other 1 c.c. of the filtrate subcutaneously. Both inoculations were followed by a positive result. One lung, taken from the rabbit that had been inoculated subcutaneously, was ground up in a mortar with normal saline and the extract filtered. The filtrate was inoculated into a second rabbit (see Passage Experiments). The kidney of the rabbit receiving the intravenous dose was placed in a Noguchi tube with ascites fluid (see Cultural Experiments).

One rabbit was inoculated subcutaneously with 2 c.c. of a filtrate of bronchial pus taken, *post mortem*, from a man who died from influenza on the twelfth day of the disease. The result was completely negative and tends to confirm our opinion that it is likely that the virus is not recoverable after the first few days of the disease.

Control. A rabbit was given 2 c.c. of a filtered sputum taken on the third day of the disease in a case of acute bronchitis. Result negative.

Guinea-Pigs. Four guinea-pigs were inoculated. Two of these were inoculated with sputum taken on the night of the second day and morning of the third day from a case of influenza. One guinea-pig was given 1 c.c. of the diluted (1–11) but unfiltered sputum, and the other received 1 c.c. of the same dilution of this sputum, filtered. In each case a positive result was obtained.

A guinea-pig inoculated subcutaneously with 1 c.c. of the filtered bronchial pus mentioned above gave a negative result.

Control. A guinea-pig inoculated subcutaneously with 1 c.c. of the filtrate of sputum from a case of acute bronchitis also gave a negative result.

Mice. Altogether, fourteen mice were inoculated with sputum, unfiltered or filtered, from various sources.

These may be divided into those inoculated with :

(*a*) Unfiltered sputum from cases of influenza.

(*b*) Filtered sputum taken during the first three days of the disease in cases of influenza.

(*c*) Heated filtered sputum taken during the first three days of the disease in cases of influenza. (Heated to 71° for half an hour.)

(*d*) Filtered sputum taken on the sixth day of the disease and later from influenza cases.

(*e*) Filtered sputum taken on the third day of the disease from a case of acute bronchitis.

Under Group (*a*) 4 mice were inoculated :
1 gave a negative result.
2 died of pneumococcal infection.
1 died of streptococcal infection.
Under Group (*b*) 5 mice were inoculated :
4 positive results.
1 was killed 24 hours after inoculation—result negative.
Under Group (*c*) 2 mice were inoculated :
2 negative results. (Mice inoculated with the same filtrate unheated all died.)
Under Group (*d*) 2 mice were inoculated :
2 negative results.
Under Group (*e*) *Control*, 1 mouse was inoculated :
1 negative result.

B. *Inoculation of Animals with Blood from Cases of Influenza.*

Experiment I. For this experiment 24 c.c. of blood were drawn off aseptically from the median basilic vein of a man who had been forty-eight hours ill with influenza. At the time the blood was taken his temperature had begun to fall, and this reached normal on the third day, after which he made an uninterrupted recovery. The blood was run off directly from the vein into a flask containing 2 c.c. of 10 per cent. sodium citrate. The blood was then divided into two parts. One part was left at room temperature, and 10 c.c. of the other was diluted with 40 c.c. of distilled water to lake the blood.

Cultures were made in the usual way, both from the whole and laked blood, and proved sterile in each case after a week's incubation. The laked blood was then passed through a Chamberland L. 1 bis filter under a negative pressure of 50 c.c. of mercury. The filtrate also proved sterile with regard to non-filtrable organisms.

A *M. rhesus* monkey (No. 8) was inoculated subcutaneously with 5 c.c. of the whole blood which had been standing at laboratory temperature for six hours. This monkey showed no symptoms up to the seventh day, after which he was killed. *Post mortem* nothing abnormal was seen, nor was any abnormality observed in its lungs on microscopical examination.

A *M. rhesus* monkey (No. 6) was inoculated subconjunctively in each eye with 0·25 c.c. of the filtrate and 0·5 c.c. was instilled up its nostrils. Five days later it was 'moping' somewhat and its temperature that afternoon rose to 108° C. The condition remained the same on the following day, and on the seventh day it was killed. The post-mortem findings were as follows :

The monkey was thin and did not appear to be well nourished.

Larynx. This was somewhat injected.

Trachea. The mucous membrane was markedly red between the tracheal rings.

Lungs. Beyond retaining their shape when placed on the table, the lungs of this animal presented no abnormal features either externally or on section when examined macroscopically.

Other organs. These were normal.

Microscopic appearances. The section of the lung showed some patchy inflammatory changes in which small groups of alveoli had become filled with inflammatory exudate, and this was already invaded by leucocytes. These areas showed some engorgement of capillaries. The leucocytic accumulation was more marked round the smaller bronchi, and some desquamation of the mucous membrane was present.

Bacteriology. Bacteriological examination of the organs of both these animals gave negative results in culture.

In addition to the above inoculations, one mouse received 0·25 c.c. of the whole blood subcutaneously (Mouse W. 1).

One mouse received 0·25 c.c. of the filtered blood subcutaneously (Mouse W. 2) and one mouse received 0·25 c.c. of the filtered blood which had been heated to 55° C. for half an hour (Mouse W. 3). Unfortunately two of the mice employed (Mice W. 1 and W. 3) were already infected with coccidiosis. The mouse receiving the unfiltered blood died during the night following on the injection. *Post mortem* the lungs appeared very haemorrhagic and small white areas were present on both lungs. Under the microscope the lung presented an acute haemorrhagic condition superimposed on coccidiosis.

The mouse receiving the filtered blood (untreated) was *killed* on the fourth day after the inoculation. *Post mortem* the lungs showed red haemorrhage-like patches on both lungs, especially on the posterior surfaces. No infection by coccidia was found in this animal.

Microscopically, the lungs were seen to be in a condition of congestion with acute inflammation with the usual exudate (see Plate IX B, Mouse W. 2). The mouse (Mouse 3) which received the heated filtrate died on the third day after inoculation. This mouse was also infected with coccidia. The lungs *post mortem* were apparently haemorrhagic and discrete white areas were present over their surfaces. Microscopically there was seen to be present a condition of acute inflammation in addition to an infection with coccidia. The bacterial investigation of the blood and lungs of these mice gave constant negative results. The last experiment points to the probability that the filtrable virus resists heating to a temperature of 55° C. for half an hour.

Experiment II. Three other mice were inoculated subcutaneously with whole blood which was taken aseptically from the median basilic veins of patients suffering from influenza. In one instance the blood was removed on the first day of the disease and in the other two on the second day. The mice in all instances were inoculated with 1 c.c. of blood subcutaneously. The inoculations were carried out in the ward in which the patient was immediately the blood was withdrawn from the vein. The mouse inoculated with the blood taken on the first day of the disease died eight days later. *Post mortem* the lungs showed definite haemorrhage-like areas over both lungs. Microscopically, the alveoli were filled with an inflammatory exudate, and there was also present congestion of the capillaries. One mouse inoculated with blood taken on the second day of the disease was killed eight days later.

Post-mortem findings. On opening the thorax the lungs were found bound down and extremely difficult to remove. They showed deep

red staining in places and were not of the usual pink colour. This condition was present on all the lobes of the lungs.

Microscopically marked inflammatory reaction was seen to be present. There was some haemorrhagic exudate scattered through the lung substance in the alveoli. The section also showed thrombosis of the vessels and marked small cell accumulation round some of the bronchi.

Another mouse, inoculated with blood taken on the second day of the disease and killed on the sixth day, showed the same haemorrhage-like patches over the lungs *post mortem*. Microscopically, there was again present acute congestion with haemorrhage into the alveoli, acute inflammation, and some leucocytic reaction.

Bacteriology. This examination gave negative results in each case.

As Controls to these three mice, two mice were inoculated with, in one case, 1·25 c.c. of normal human blood, and in the other, 1 c.c. of normal human blood. In neither instance was an abnormality found *post mortem* either macroscopically or microscopically.

Experiment III. This experiment was undertaken to attempt to obtain information as to the earliest time after inoculation into mice of blood from influenza cases that one may expect to find any pathological lesions in the lungs of those animals. Six mice were inoculated, each with 1 c.c. of blood taken from a case of influenza during the first twenty-four hours of the disease. These mice were each given 1 c.c. of blood subcutaneously, and it was intended to kill these animals at varying intervals up to eight days after inoculation. However, this intention was frustrated by the fact that five out of the six mice died during the first forty-eight hours after they received the injection.

The results are best shown in tabular form :

No. of Mouse.	*Inoculated.*	*Died.*	*Appearance of lung Post-M.*
U. 1	2.12.18	Same night	Lungs showed nothing abnormal (inoculated intraperitoneally).
U. 2	,,	Next morning	Both lungs showed haemorrhagic-like patches.
U. 3	,,	Same night	Nothing abnormal seen in lungs (inoculated intraperitoneally).
U. 4	,,	Next morning	L. lung showed haemorrhagic-like patches.
U. 5	,,	Night of 3.12.18	Haemorrhagic-like patches on both lower lobes.
U. 6	,,	Killed 3.12.18	Lungs apparently normal.

Of the six lungs examined microscopically, two showed acute inflammatory reaction with congestion in one instance. Of the remainder, three showed acute congestion only and one some leucocytic infiltration.

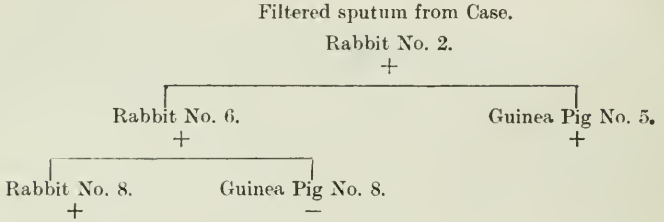
C. *Passage of the Virus from Animal to Animal.*

Filtered sputum from an early human case of influenza was administered to a group of two monkeys (Nos. 11 and 7), two rabbits (Nos. 1 and 2), and two mice (Nos. Z 1 and Z 2) on December 9, 1918. Of this group, Monkey 7 received no injection but the filtered sputum was merely instilled into the nose. This animal remained

negative. Mouse Z 2 was given an injection of *heated* filtrate and, as was to be expected, remained negative.

All the other animals were inoculated with the unheated filtrate and all gave positive results.

Of these animals rabbit 2 was selected to provide material for passage experiments.



Rabbit No. 2. The history of this rabbit was as follows :

9. 12. 18. *Subcutaneous inoculation of* 1 *c.c. of filtrate from sputum.* No symptoms of illness noted after inoculation.

15. 12. 18. Killed and examined *post mortem.*

Findings. The lower lobes of both lungs showed purplish discoloration and haemorrhagic areas. Microscopically, irregular acute inflammatory changes, with early leucocytic reaction, were noted in sections of the lungs, together with engorgement of the capillaries.

Bacteriological examination of the lungs was negative so far as concerns non-filterable organisms.

The lower lobe of the left lung of this rabbit was now removed, crushed, extracted with normal saline, and the extract passed through a Chamberland F. Filter and used as the inoculum for further passage experiments, being injected into rabbit No. 6 and guinea-pig No. 5.

Rabbit No. 6.

15. 12. 18. *Subcutaneous inoculation of* 2 *c.c. of filtered lung extract from rabbit No.* 2.

23. 12. 18. Killed and examined *post mortem.*

Findings.

Trachea. There is found some tracheitis in the lower part of the trachea which is filled with a frothy blood-stained fluid which oozes up from the bronchi.

Pleura. Some fluid present in each pleural sac.

Lungs. Retain shape on being stood on the table. The anterior surface of the right lung shows a patch of haemorrhage at the root of the upper lobe. The anterior surface of the left lung presents very little abnormality. The posterior surface of both lungs is uniformly of a dark red colour. On section, the lung substance is seen to be reddish-brown in patches and some frothy blood-stained fluid drips from the cut surface. Cultures on blood-agar and glucose broth were found to be sterile so far as regards non-filtrable germs. Lung substance from this animal was emulsified and inoculated into rabbit No. 8 and guinea-pig No. 8.

Guinea-Pig No. 5.

15. 12. 18. *Subcutaneous inoculation of* 2 *c.c. of filtered lung extract from rabbit No.* 2.

23. 12. 18. Killed and examined *post mortem.*

Both lungs were found to show large dark-red patches over both anterior and posterior surfaces.

Rabbit No. 8.

23. 12. 18. *Intravenous inoculation of* 2 *c.c. of lung extract from rabbit No.* 6.

Died about one hour after inoculation.

24. 12. 18. *Post-mortem examination. Peritoneal cavity* clear and glistening. Bowel generally pale and yellowish.

Trachea. The upper part shows the blood-vessels between rings outlined in deep red, and an extreme degree of congestion seems to be present between all the cartilaginous rings. Frothy fluid wells up in the trachea from the bronchi.

Pleura. No evidence of pleuritis on either side. No fluid present.

Lungs. Both lungs appear much the same. Generally they are pink with an overlying crimson and deep red coloration which looks haemorrhagic. It seems, in the gross, to be an extreme grade of what has previously been seen in infected rabbits' lungs.

On section, the surface drips bloody fluid and shows numerous deep red small haemorrhagic areas on the cut surface.

Thymus. Enlarged. Soft. Vessels deep red and engorged. Large numbers of deep purple haemorrhages seen on surface.

Kidneys. Deep red. Drip blood on section. Capsule strips easily.

Liver. Deep red. On section, blood drips from surface and lobules appear outlined in deep red.

Guinea-Pig No. 8.

23. 12. 18. *Subcutaneous inoculation of* 2 *c.c. of lung extract from rabbit No.* 6.

31. 12. 18. Killed and examined *post mortem.*

The lungs and other organs appear to be normal.

Remarks. In the above series of experiments a tendency to increase of virulence was noted in passage through rabbits. The lesions found in rabbit No. 2 were of only moderate severity. Those produced in rabbit No. 6 by inoculation of material from rabbit No. 2 were much more severe. The inoculation of lung extract from rabbit No. 6 into rabbit No. 8 led to the rapid death of the latter, the symptoms and post-mortem appearances being very striking and suggesting that the inoculum may have contained a toxin of high virulence in addition to the living virus. It should be noted that this animal received an intravenous inoculation, so that any toxin introduced would have been rapidly distributed throughout the organism. It is a remarkable thing, however, that an equivalent amount of the same lung extract proved harmless for guinea-pig No. 8, inoculated at the same time as rabbit No. 8. This result may perhaps be explained by assuming that this guinea-pig was unusually resistant to the virus and its toxin. It is to be noted, too, that, in this instance, the injection was subcutaneous, not intravenous.

C. *Cultural Experiments and Inoculation of Cultures into Animals.*

In view of apparently positive results we had obtained in the transmission of influenza to animals by means of filtered materials,

blood, sputum, &c., from cases of influenza, it was decided to attempt to obtain cultures of the virus by means of the method used by Noguchi. We had always obtained uniformly negative results in attempting to culture different filtrates, using the ordinary media employed by us in investigating the bacteriology of sputum, post-mortem material, &c., from cases of influenza, i. e. serum broth, blood agar, heated blood agar, &c., but the Noguchi technique still remained to be tried.

In November 1917 Foster reported (*Journal of Infectious Diseases*, Vol. xxi, No. 5), that in studying the etiology of common colds he had been able to isolate an organism by means of Noguchi's methods, and that he had reproduced the disease in human beings by means of nasal instillation of his culture. His method and technique are described in great detail in his monograph, and we have followed them as closely as possible in a laboratory in the Field. Although the work is incomplete, we consider that the results are definite enough to warrant publication.

(a) *Preparation of Noguchi culture tubes.* At first we had great difficulty in obtaining a supply of ascites fluid, and our earlier experiments were made with human blood serum with negative results. This is not surprising as it is recognized that blood serum tends to inhibit the growth of filtrable organisms, that of poliomyelitis being an example.

Finally a case of general polyserositis occurred and a litre of clear amber-coloured ascites fluid was obtained and proved to be sterile.

Special tubes were obtained measuring 1 cm. × 20 cm. These were sterilized by hot air and filled with ascites fluid to within 6 cm. of the top. These tubes were then allowed to stand five days at 37° to eliminate the possibility of contamination.

A rabbit was now anaesthetized with ether and the neck vessels severed with a sharp bistoury and as much blood as possible allowed to drain away. It was then stretched out on a board and thoroughly drenched with strong iodine solution.

Scissors, forceps, and scalpels had been sterilized in three separate packets for use at different stages in removing the kidney of the rabbit.

The skin was incised in the mid line from the neck to the tail and carefully stripped back from the abdomen and thorax and fastened down to the board. The tissues were again drenched with iodine.

A semi-lunar line curving outward, about 2 cm. wide, was thoroughly seared from the costal margin to the groin.

Another packet of instruments was opened and the abdomen slit open along the seared line and the two edges of peritoneum held back with rat-tooth forceps by an assistant. Meanwhile another packet of instruments had been opened. The bowels were pulled through the opening with the hand covered with sterile gauze and the kidneys picked up with a pair of forceps and quickly removed with scissors and transferred to a sterile petri-dish.

The kidney was then cut up with sterile scissors into small cubes just large enough to enter the culture tube easily, the lid of the dish being held over the instruments by an assistant while this was being done.

The tubes were then opened one by one and a piece of kidney put into each with a hot platinum wire and allowed to fall to the bottom of the tube. Sterile liquid paraffin was then poured into each tube to within 2 cm. of the top, the tube was plugged, and a rubber cap put on.

These tubes were allowed to stand for one week before being used.

When cultures were made the material to be cultured was drawn up into a long teated capillary pipette and then expelled until it had formed a drop on the tip, when the pipette was quickly plunged through the paraffin and ascites fluid to the kidney and the material all expelled to within 3 or 4 cm. of the tip. The pipette was now withdrawn quickly and the tube plugged again.

(b) *Staining methods.* When it was desired to examine microscopically material from the bottom of the tube, this was obtained with a capillary pipette and the pipette broken off above any oil that might have clung to it. A few drops were then placed on a slide, spread slightly, and allowed to dry in the open air upside down.

They were fixed for one hour in pure methyl alcohol and stained for twenty-four hours in 5 per cent. Giemsa stain, always having the smear downward to prevent any stain from depositing.

Foster stated that one should see in uninoculated tubes in twenty-four to forty-eight hours only a clear zone of haemolysis above the kidney, and possibly a very faint opalescent zone, but nothing more, and we have confirmed this. Even the haemolytic zone may be very faint if the animal from which the kidney was removed had been thoroughly exsanguinated.

When we first commenced the cultural work in December 1918 we were temporarily somewhat short of animals. This fact led to our obtaining our first culture from the kidney of an infected animal instead of directly from the material from human cases. This came about in the following way :

Wishing to prepare some Noguchi tubes, and having no normal rabbits from which to obtain the tissues, we used the kidney from a rabbit that had been inoculated with a filtrate of influenza sputum and which had reproduced the characteristic signs in its lungs. The Noguchi tubes thus prepared were placed in the incubator to ensure their sterility.

In twenty-four hours a clear pale-red zone had developed above the tissue, and in forty-eight hours it was noticed that a faint cloud was appearing. In seventy-two hours this had increased, and a week later the cloud was about 3 cm. high and a fine deposit had begun to settle on the bottom of the tube.

The cloud showed no tendency to blend with the clear ascites fluid above and was rather more dense immediately above the kidney. The culture was examined by subculturing for the presence of any non-filtrable contamination, and this was found to be absent.

On the thirteenth day a smear was made and stained with 5 per cent. Giemsa stain for twenty-four hours after fixation in methyl alcohol for one hour. In this smear the following appearances were noted :

Numerous small coccoid bodies in size varying from about 0·1μ to 0·2μ and generally single, but often taking on a diplococcal arrangement and sometimes occurring in small agglomerations.

Some showed a rather delicate halo, the significance of which has not been determined.

With Giemsa, they usually stained a deep purple, but some which were apparently degenerate were paler in colour and of a pinkish tinge.

On this particular occasion the cocci was Gram-negative, but it has since been shown that in young cultures Gram-positive organisms may be found.

The cloudy material was transferred to other Noguchi tubes and the same phenomena occurred. Smears made from the resulting subcultures, stained with Giemsa, showed the same picture as described above.

(c) *Animal Experiments with Cultures.*

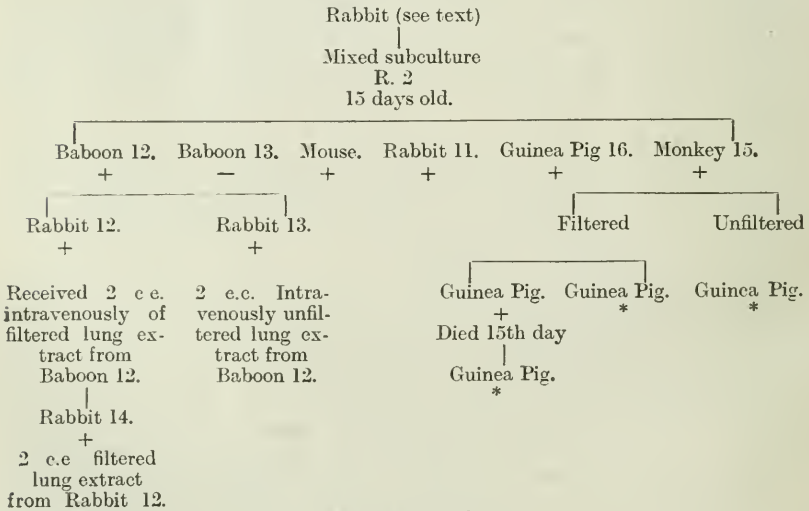
Experiment I. Original cultures were put up on December 15, 1918.

On December 28, when the cultures were thirteen days old, a mouse was inoculated subcutaneously with 0·25 c.c. of the original culture. It died six days later. Its lungs showed some haemorrhagic areas.

Post mortem. Its kidneys were removed with aseptic precautions and implanted in a Noguchi ascites fluid tube. A subculture was obtained, but not proceeded with farther. A rabbit was also inoculated intravenously with 1 c.c. of the culture. It was killed seven days later and, although the lungs of the animal did not show any typical signs of a marked infection, a culture was obtained from the rabbit's kidney.

In addition to these animal inoculations, subcultures of this virus were made on December 28 and a definite cloud was obtained. Fifteen days later, on January 12, 1919, these cultures were mixed together and the following animals were inoculated as shown in table:

Original Culture.



\+ = A positive result.
* = Still under observation.

At the same time as the animals were inoculated the subculture Rabbit 2 was inoculated into another Noguchi tube. This culture produced the usual cloud and the smear showed the presence of the typical coccoid bodies.

Thus the third generation by direct subculture has been reached and at the time of writing it has not yet been taken farther.

Besides these experiments we have also succeeded in growing the organism: (1) From a filtered sputum from a case of influenza; this also has been carried through to the second generation. (2) From the filtered lung extract of Baboon 12. (3) From the kidney of another infected animal.

Controls. On the other hand, the kidneys from normal rabbits when cultured in Noguchi tubes have failed to produce these organisms on culture, as also the kidney from a monkey inoculated with sputum from a case of simple acute bronchitis.

V. Conclusions.

The number of experiments carried out by us is too small to justify the drawing of final conclusions. These experiments were brought to an end by the cessation of the epidemic, and the loss of laboratory attendants consequent on demobilization. We feel, however, that we are in a position to make the following deductions from our work:

I. The apparent immunity of some animals to filter-passing viruses and the occasional difficulty of the transmission of these viruses by means of blood is well known. When this is taken into account the number of positive results obtained by us would seem to be significant.

II. The pathological lesions in what may be called experimental influenza in animals closely resemble those seen in the lungs of men.

III. There is some evidence in favour of the view that the passage of the virus from one animal to another may raise its virulence.

IV. Inoculation of the filtered and unfiltered sputum taken from cases of influenza, especially at an early stage of the disease, has been found to produce lesions in the lungs in a high proportion of inoculated animals. The inoculation of blood may not always produce such striking results.

V. A minute coccoid micro-organism may be grown by Noguchi's cultural methods from:

(*a*) The kidney of infected animals;
(*b*) The filtrates of lung tissue; and
(*c*) The filtered sputum from cases of influenza.

The cultures have been carried by us to the third generation by direct culture. The cultures when inoculated into animals produce typical 'experimental influenzal' lesions, and cultures can be recovered again from the animals so inoculated, either by direct culture or by filtered extracts of the organs.

VI. In view of these findings we consider that there are very strong grounds for considering that:

(*a*) the organism isolated by us is capable of passing through a filter, and

(*b*) that it is in all probability the cause of influenza as seen to-day.

A similar organism, having the same properties, has already been described by Captain J. A. Wilson, R.A.M.C., working independently at No. 20 General Hospital.[3] We had completed our investigations before his research came to our knowledge. Since the publication of his work on this subject, we have shown him our preparations and he considers our organism to be the same as his own, in which opinion, after examination of his slides, we are in agreement.

We are indebted to the Medical Research Committee for providing the material for the work, to Colonel S. L. Cummins, C.M.G., A.M.S., Adviser in Pathology, British Armies in France, for valuable advice ; to the O.C.s of No. 2 Stationary Hospital and No. 3 Australian General Hospital for allowing us the use of the laboratories attached to their hospitals, and to the O.C., No. 2 Stationary Hospital, for the use of his wards.

The help of Pte. Webster, A.I.F., and Pte. Whally, R.A.M.C., has been invaluable in the care of the animals, and our thanks are also due to Pte. Urquhart, R.A.M.C., our laboratory attendant, for much hard work in the preparation of media.

NOTE BY COLONEL S. L. CUMMINS,

Adviser in Pathology, British Armies in France.

While Major H. G. Gibson, R.A.M.C., was actually engaged in preparing the above Summary of the work of the Influenza Research Team, of which he was the Senior Officer, he was, himself, attacked by the disease in its severest form. He had been working for long hours in the laboratory at cultural and passage experiments with the organism believed to be the ' Filtrable Virus ' of influenza, and the attack found him overdone and weary from his self-forgetting efforts to solve a problem of pressing military and general importance.

His death, a grievous loss to Medical Science and to the Royal Army Medical Corps, was still such an end as a soldier would have chosen. Laborious tasks cheerfully undertaken and dangers resolutely faced are no less glorious in the laboratory than in the trenches.

Major Gibson had no opportunity of revising or even finishing his Summary, which has had to be completed from his notes and records. Any obscurities or redundancies are therefore to be attributed, not to him, but to the sad circumstance that others had to arrange his work for publication.

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2. THE BACTERIOLOGICAL FLORA OF THE RESPIRATORY TRACT IN CASES OF INFLUENZA

BY

Major H. G. Gibson, R.A.M.C.

AND

Major F. B. Bowman, C.A.M.C.

Although careful studies have been made of the sputum and material from the naso-pharynx in cases of influenza in widely separated areas, these have in many instances been contradictory. It was decided to investigate this problem in the series of cases being studied clinically for this report. The findings will be found briefly under the descriptions of the individual cases. However, it may be of interest to make a few general remarks regarding the work done.

In many cases of influenza it was impossible to obtain a specimen of sputum in the first few days of the disease and from these only a swab from the throat was made.

I. Methods.

A. *Culture Media.*

For all primary cultures human blood agar plates were used. To be of any practical value as regards the presence or absence of haemolysis they must be made very carefully. Ordinary plain agar with a reaction of about plus six is prepared and kept in stock. When plates are to be made the flask of agar is melted and the temperature reduced to 50°, when defibrinated human blood is added in the proportion of 5 per cent. and well mixed, and plates are then poured. Defibrinated blood is preferable to citrated blood, and the serum should not be removed as this aids in a clear-cut haemolytic reaction. Care should be taken that the agar is not too hot when the blood is added, as some alteration in the cells occurs which interferes with haemolysis. Any carbohydrate in the medium may mask the result by the production of acid with a resulting brown coloration.

For subcultivation of *B. influenzae* the following medium was used. This was first recommended by Fitzgerald (*Centralbl. f. Bakteriol*, 56. 464). Flasks of agar are prepared as above and defibrinated human blood added in the same proportion and the whole brought to a temperature of 80°, when the medium assumes a homogeneous non-granular chocolate colour. On this medium the organism grows profusely.

Levinthal's medium is also of value, and has the advantage of being clear; but often a batch, although made very carefully, will fail to grow the organism, and for this reason we gave up its use entirely.

Fildes states that this difficulty may be obviated by the use of glass wool in filtering (*Lancet*, November 23, 1918).

For stock cultures of *B. influenzae* (Pfeiffer) a little defibrinated blood is added to a meat broth tube and heated to 80° C. Transplants are not necessary more often than once a month using this method. (This was recommended by Captain Perry, R.A.M.C., and Captain Fleming.)

In an attempt to obtain a clear medium for the growth of *B. influenzae* and streptococci the following method was used, and although it failed in so far as a profuse growth of *B. influenzae* was concerned, a rather interesting phenomenon occurred.

A 1 per cent. solution of saponin was made in distilled water and defibrinated blood was added to this until no more dissolved, when a very concentrated solution of haemoglobin resulted which was almost black in colour. This was added in different amounts to agar, but the results were not encouraging so far as haemolytic reaction of streptococci were concerned, although *B. influenzae* grew quite well. In attempting to find a clear fluid medium which would differentiate between so-called green or brown haemolysis and clear haemolysis, a little of this ' saponized ' blood was added to plain broth tubes until they assumed a pale cherry red colour. Cultures of streptococci were seeded into this medium and it was found that those belonging to the *viridans* group could be separated from the haemolytic group quite easily. *Streptococcus viridans* produced a definite dirty green colour in marked contrast to the haemolytic group, where little change in colour was noted but a profuse growth occurred.

We also found that this concentrated haemoglobin solution when added to agar and heated to 80° C. produced a useful medium for the growth of *B. influenzae*.

For the preparation of carbohydrate media for the classification of streptococci see below under blood cultures.

II. Material Examined.

A. *Sputum*.

This was obtained from the patient in a clean vessel. If possible it was collected for twenty-four hours.

We have found that samples from true cases of influenza have a characteristic appearance and from this alone we almost could foretell the presence or absence of *B. influenzae*. It usually appeared rather homogeneous and creamy and not in large greenish white lumps and flakes. In colour it was pale greyish yellow with sometimes a faint rusty tinge. It was extremely tenacious and elastic, and when picked up with a wire stretched out into long threads.

A small globule of sputum about the size of a pea was transferred to a petri dish and washed thoroughly in several changes of distilled water, any superfluous water being absorbed by strips of blotting paper. The sputum was then torn into small fragments with forceps, and one of these was transferred to a blood agar plate and carefully streaked with a platinum wire. Another small portion was smeared on slides for staining by Gram's method, and for capsules.

B. *Naso-Pharyngeal Swabs.*

In making cultures from throats sterile West swabs were used. These were smeared carefully on one side of a blood agar plate and streaks were made from side to side with a platinum wire.

C. *Post-Mortem Material.*

Bronchial fluid. The trachea and lungs having been removed entire, the trachea was carefully opened and the lungs lifted up and any material flowing past the bifurcation caught in a test-tube and taken to the laboratory. Here smears and cultures on blood agar were made as was done with the sputum.

Tracheal scrapings. The trachea was wiped dry with gauze and the inflamed mucous membrane scraped with a knife and the material transferred to a test-tube. It was then examined fresh and cultures made.

Lung cultures. A portion of lung was taken to the laboratory and seared and cultures made with a loop on to blood agar.

Pericardial fluid and heart's blood. Were removed with sterile pipettes after searing and taken to the laboratory for culture into serum broth and on to blood agar plates.

Any other material was treated in the same way.

III. Results of Bacteriological Examination.

It is interesting to note that early in this epidemic we had some difficulty in the preparation of our carbohydrate media, and until this was adjusted organisms were described as pneumococci or streptococci simply on morphological grounds and the reaction on blood agar. The result was that some cases were reported as having pneumococci in the sputum when, as shown by our later work, the organism was probably a streptococcus. The cultures and smears taken from post-mortem material were noted in the same way.

The marked pleomorphism shown by certain organisms even in fresh smears made observations very misleading. In certain specimens of sputum examined, typical pneumococci (capsulated), diplostreptococci (with capsules), and smaller streptococci were found. On culture only one type of colony appeared. This was a rather dry crater-like flat colony sometimes with irregular edges, showing no haemolysis and with a certain amount of greenish-brown coloration around it. Smears in twenty-four hours showed it to be a lanceolate diplostreptococcus, and the same colonies examined in four days showed extremely marked pleomorphism, cocci large and small, clubbed forms, flattened and round streptococci were observed and in fact almost every form imaginable. Thus it can be easily seen that from morphology alone it would be utterly impossible to classify organisms as pneumococci or streptococci as seen in stained specimens of sputum. The same statement would apply to material removed from other sources where the same organisms were found.

Material obtained from twenty-four post-mortem examinations was examined bacteriologically by methods cited elsewhere.

Bronchial Fluid : 25 Cultures.		
B. influenzae (Pfeiffer)	17 times	or 68%
Streptococcus viridans	22 „	88%
Haemolytic streptococcus (not associated with *B. influenzae*)	4 „	16%
Lung : 19 Cultures.		
B. influenzae (Pfeiffer)	6 „	32%
S. viridans	16 „	84%
Haemolytic streptococcus	3 „	16%
Pericardial Fluid : 20 Cultures		
B. influenzae (Pfeiffer)	0 „	
S. viridans	1 „	5%
Haemolytic streptococcus	3 „	15%
Heart's Blood : 6 Cultures.		
S. viridans	1 „	17%
Tracheal Scrapings : 13 Cultures.		
B. influenzae (Pfeiffer)	11 „	85%
S. viridans	12 „	90%
Haemolytic streptococcus	1 „	8%
Tracheal Glands : 10 Cultures.		
All negative with the exception of 1 where a haemolytic streptococcus was isolated, but this was found in all other material examined from this case		10%
Pleuritic Fluid : 5 Cultures.		
B. influenzae (Pfeiffer)	1 „	20%
Haemolytic streptococcus	1 „	20%
S. viridans	2 „	40%

From a post-nasal abscess in one case a profuse growth of *B. influenzae* resulted, accompanied by *S. viridans*.

Six subclasses of streptococci were found in our investigation of thirty-six stains (see Table II for fermentative reaction of these).

For classification of thirty-six stains of streptococci showing sources from which they were obtained see Table III.

26 or 72 per cent. belonged to the *viridans* group and of these 58 per cent. gave the reactions of *Streptococcus mitis*.

The absence of pneumococci from our cultures is remarkable in view of the work of others. By some workers the pneumococcus has been described as the predominant organism found in the material examined. We were led astray as stated before, early in our work, by identifying organisms on morphology alone, but later when ' typical ' pneumococci were found they were tested for bile solubility and put up against standard type agglutinating sera and in only two instances were the original classifications confirmed.

From twelve specimens of sputum examined, *B. influenzae* (Pfeiffer) was isolated eight times (see Table V) and always associated with a streptococcus of the *viridans* group in numbers that would suggest that they might possibly have played some part in conjunction with *B. influenzae* in the causation of secondary infections.

The question of symbiosis of *B. influenzae* with other organisms has been suggested by different workers. We found that it grew profusely with a streptococcus of the *viridans* group and was still alive after two weeks at room temperature. There seems little doubt that symbiosis exists and may account for the number of times the organism has been grown easily in association with the peculiar streptococcus mentioned above.

The following experiment rather graphically illustrated this fact. Streaks from an emulsion of Pfeiffer's bacillus were made on a blood agar plate about a centimetre apart, and at right angles to these streaks were made with a culture of *S. viridans*. Where the lines crossed it was found that Pfeiffer's bacillus had grown much more profusely than along the streaks.

IV. Results of Blood Culture in Twenty Cases of Influenza.

Blood cultures were made from the twenty cases of influenza studied clinically for this report.

The technique employed was the following:

Media Employed.

(a) *Human blood agar.* (For preparation see under methods previously described.)

(b) *Glucose serum broth* was prepared with horse serum. This was obtained by bleeding horses from the jugular vein into sterile Winchester quart bottles and allowing the blood thus obtained to clot. The serum was then drawn off and an equal quantity of normal saline was added, after which the mixture was passed through a Doulton filter.

The glucose broth was made up according to the formula quoted below after that given by Holman for his carbo hydrate serum broth.

Double strength trypsin broth prepared according to Douglas' method	(+12 acid) 200 c.c.
Distilled water.	100 c.c.
Glucose	4 gram.

Flasks of this medium were prepared, each containing 25 c.c., and to each of these was added 16·5 c.c. of the diluted and filtered serum.

The patients were bled from one of the veins at the bend of the elbow and 2 c.c. of blood were sown into the flasks of serum broth, also a drop of blood was smeared on the surface of blood agar.

In some cases the glucose serum broth was incubated both aerobically and anaerobically, but in no instance was a growth obtained under anaerobic conditions when a negative result was obtained in aerobic culture.

Table I shows the day of disease in each case in which blood cultures were made and the number of positive results obtained.

The cases in which only one or two observations were made were cases which were of a milder nature and rapidly recovered.

Three cases out of twenty gave positive results with blood culture. Two of these positive results were obtained within a short time of death, that is in Cases Nos. 1 and 3, the first dying on the seventh day and the second on the fifteenth day. In both these cases the preliminary cultures proved sterile, and Case No. 18 was the only one in which a positive blood culture was obtained any length of time before the fatal termination of the illness.

Table I.

Days of Disease.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	*Final disposal of Case.*
Case No. 1				—			+ ‡														Died
,, 2				—																	Recovered
,, 3				—		—			—				+		‡						Died
,, 4					—																Recovered
,, 5					—							—								—	,,
,, 6				—																	,,
,, 7	—																				,,
,, 8			—																		,,
,, 9				—																	,,
,, 10						—					—					‡					Died
,, 11				—																	Recovered
,, 12		—																			,,
,, 13						—					—				—				‡		Died
,, 14				—																	Recovered
,, 15			—						—		‡										Died
,, 16				—	—																Recovered
,, 17								—													,,
,, 18		+			—																,,
,, 19		—																			,,
,, 20		—		—																	,,

‡ Patient died on this day.

The organism recovered was in each case a Gram-positive diplostreptococcus which grew on blood agar as small flat crater-like colonies producing no haemolysis, but imparting a brownish green tinge to the media.

They showed extreme pleomorphism in cultures which were a few days old.

In glucose broth they produced a uniform turbidity with a granular deposit. None were bile soluble.

Following Holman's formula the streptococci isolated all belonged to the *viridans* group, that from Case No. 1 giving the reactions of *S. faecalis* and those from Cases Nos. 3 and 18 of *S. mitis*.

In no case was *B. influenzae* recovered from the blood stream.

From these thirty-two attempts at blood culture it would appear that streptococci rarely enter the blood stream in the early stage of the disease, and usually their presence there may be taken as a terminal phenomenon.

In Case No. 18 a streptococcus was recovered on what was apparently the second day of the illness, but the patient may have had the disease for a few days previous to this. The organism was not recovered at a second attempt.

V. Agglutination Reactions.

In view of the fact that *B. influenzae* (Pfeiffer) has been found constantly in the sputum of cases of influenza and in material removed *post mortem*, the question of specific agglutination arises, and this was studied in twelve cases.

These were selected at different stages in the course of the illness from two to twenty-five days.

The organism was grown on heated blood agar, washed off with 0·85 per cent. saline, and any extraneous matter allowed to settle. The supernatant suspension was then decanted, well shaken, and diluted to pale opalescence with saline.

Several methods of performing reaction were tested.

1. Using fresh suspensions of *B. influenzae*.
2. Using carbolized suspensions.
3. Using formalinized suspensions.

The suspension with serum in different dilutions were placed in the water bath at 37° C. and 55° C.

The only well-defined results were obtained with formalinized cultures in the water bath at a temperature of 55° C.

By consulting Table VI the result may be seen briefly.

The most marked reactions were obtained between the second and sixth day inclusive, and the strongest reaction of all was obtained in a second-day case.

It might be noted also that in some instances the higher dilutions gave the most marked agglutination reactions, although these were not continued to the limit of agglutinability.

VI. Summary.

The bacteriological investigations of cases of influenza were begun before we had seen the work of Nicolle and Lebailly, and although

there seems to be little doubt that none of the primary symptoms in this disease are caused by any of the organisms described in this section, their importance as secondary invaders cannot be denied. For this reason the work was continued after we had obtained positive results in our animal experiments with filtered material from cases of influenza.

The following conclusions may be cited briefly :

(1) *B. influenzae* (Pfeiffer) is usually present in the respiratory tract of cases of influenza. It was found in 67 per cent. of specimens of sputum and somewhere in the respiratory tract of 80 per cent. of cases examined *post mortem*. Most commonly it was found present in material scraped from the inflamed trachea and in fluid welling up into the larger bronchi. In haemorrhagic areas in the lungs it was seldom found. It was isolated once from pleural exudate, and in almost pure culture from a post-nasal abscess in one instance. Blood cultures were uniformly negative in regard to this organism as well as cultures from the heart's blood and pericardial fluid.

(2) Following Holman's formula for the classification of streptococci, we have found commonly present a diplostreptococcus, showing marked pleomorphism and belonging to the *viridans* group. In 88 per cent. of examinations of post-mortem material it was found, and equally common in the bronchial fluid, tracheal scrapings, haemorrhagic areas in the lungs, &c. Morphologically, at times it might have been called a pneumococcus, but agglutination with type sera and tests for bile solubility disproved this.

(3) Haemolytic streptococci were very uncommon in our series. Only five strains were isolated from twenty-five post-mortems.

(4) A symbiotic relationship between *B. influenzae* and *Streptococcus viridans* seems probable.

(5) Agglutination reactions as regards *B. influenzae* show that the most marked reaction with patients' serum occurs between the second and sixth day of the disease. Agglutination may be more marked in the higher dilution than in the lower.

(6) Agglutinative reactions with patients' serum and an emulsion of *Streptococcus viridans* were uniformly negative.

(7) The absence of pneumococci in our series seems remarkable in view of the work of others and the possibility of the preponderance of certain organisms in certain areas is worthy of consideration.

Table II.

Streptococci Isolated by us from Cases of Influenza Classified according to Holman.

\+ = fermentation or haemolysis.

Organism.	*Lactose.*	*Mannite.*	*Salicin.*	*Haemolysis.*	
S. mitis	+	—	+	—	*Viridans* group.
S. faecalis	+	+	+	—	
S. salivarius	+	—	—	—	
S. anginosus	+	—	—	+	Haemolytic group.
S. haemolyticus ii	—	+	+	+	
S. pyogenes	+	—	+	—	

Table III.

Thirty-six Strains of Streptococcus Typed according to Holman.

Source.	*S. mitis.*	*S. faecalis.*	*S. salivarius.*	*S. anginosus.*	*S. haemolyticus* ii.	*S. pyogenes.*
Naso-pharynx . .	2	1	1	2	1	..
Sputum	1	1	2	1	..	2
Tracheal scraping . .	1	1	..	..	..	1
Bronchial fluid . .	4	2	2	..	..	2
Lung	3	..	..	..	..	..
Pleural exudate . .	..	..	..	..	1	..
Heart's blood. . .	..	..	..	..	..	..
Pericardial fluid . .	1	..	..	..	1	..
Tracheal gland . .	..	..	..	..	1	..
Blood culture . .	2	1	..	..	..	..

Table IV.

Bacteriology of Twenty-five Post-mortem Examinations.

P. = *B. influenzae* ; V. = *S. viridans* ; H. = *S. haemolyticus* ; O. = No observation made.

P.M.	*Bronchial fluid.*	*Lung.*	*Tracheal scraping.*	*Tracheal gland.*	*Heart's blood.*	*Pericardial fluid.*	*Pleural exudate.*
1	P.V.	P.V.	O.	O.	O.	O.	O.
2	H.	H.	O.	O.	O.	O.	O.
3	P.V.	V.	O.	O.	O.	O.	O.
4	P.V.	V.	O.	O.	O.	O.	O.
5	V.	V.	O.	O.	O.	O.	O.
6	P.	O.	O.	O.	O.	O.	O.
7	P.V.	O.	O.	O.	O.	Neg.	O.
8	V.	O.	O.	O.	O.	Neg.	O.
9	P.V.H.	P.V.H.	O.	O.	O.	H.	O.
10	H.	O.	P.	H.	O.	H.	O.
11	P.V.	Abscess P.V.	O.	Neg.	O.	V.	O.
12	V.	O.	V.	Neg.	O.	V.	O.
13	V.	V.	P.V.	Neg.	Neg.	Neg.	O.
14	P.V.	V.	P.V.	Neg.	O.	Neg.	O.
15	P.V.	V.	P.V.	Neg.	O.	Neg.	O.
16	P.V.	V.	P.V.	Neg.	O.	Neg.	O.
17	V.	V.	P.V.	Neg.	O.	Neg.	O.
18	P.V.	Neg.	P.V.	Neg.	Neg.	Neg.	Neg.
19	P.V.	Staph.	V.	Neg.	O.	Neg.	Neg.
20	P.V.	V.	P.V.	Neg.	O.	Neg.	Neg.
21	P.V.	P.V.	P.V.	O.	Neg.	Neg.	P.V.H.
22	P.V.	V.	*M. catarrhalis* (pure)	O.	Neg.	Neg.	O.
23	V.H.	P.V.H.	P.V.H.	O.	Neg.	Neg.	O.
24	P.V.	P.V.	P.V.	O.	Neg.	Neg.	O.
25	P.V.	O.	O.	O.	O.	Neg.	V.

Table V.

Bacteriology of Sputum from Twelve Cases of Influenza taken between the First and Fourth Days of the Disease.

Case.	1	2	3	4	5	6	7	8	9	10	11	12
B influenzae . .	+	+	—	+	+	—	+	—	+	—	+	+
S. viridans . .	—	+	I	+	+	+	+	+	+	+	+	+
S. haemolyticus .	—	+	—	—	—	—	—	—	+	—	+	—
Gram-negative Diplococci * . .	+	+	—	—	+	+	+	—	+	+	—	—

* Unfortunately we were without type agglutinating sera for meningococci for some time, and the organisms found are classified as Gram-negative diplococci.

Table VI.

Agglutination Reactions.

Case.	*Day of Disease.*	*Serum Dilution.* 1/20	1/40	1/80	1/160	1/320	1/640
We.	2nd	+	++	+	+	+	±
Pi	,,	±	±	+	+	±	±
Pr.	,,	++	+++	+++	++	++	++
D.	6th	+	+	+	++	++	++
B.	,,	++	++	0	++	++	+
J.	,,	+++	++	+	+	±	+
Ch.	7th	+	+	—	+	—	—
Wa.	12th	—	—	—	—	—	—
Gr.	16th	—	—	—	—	—	—
Fa.	20th	—	—	—	—	—	—
Ca.	16th day after relapse	±	—	±	+	+	++
Tu.	25th	—	—	—	—	—	—

3 (*a*). A STUDY OF TWENTY CASES OF INFLUENZA, CLINICALLY

By Major C. E. SUNDELL, R.A.M.C.

I. Source of Material.

The cases upon which this report is based were drawn from those admitted to this hospital during October and November 1918.

Two series are included :

(1) Special—twenty cases in which full pathological records are available for correlation with the clinical findings.

(2) General—1,000 cases in which, though investigations were incomplete, certain points of interest were considered in detail.

The patients in both series include British officers and other ranks and German prisoners of war : in the general series the large majority was made up of German prisoners of war.

II. Types of Case.

These were trivial, mild, or severe. It was noteworthy that the proportion of severe cases was at its height during the middle third of the epidemic, and that the severity of the disease diminished considerably before the actual incidence of the disease itself diminished.

III. Age of the Patient.

The population from which our patients were drawn was composed of men between 19 and 50—most of them between 20 and 35. It appeared that (1) the disease was much more prevalent among the young and (2) the severe type of the disease was much more prevalent among the younger than among the older men.

IV. Clinical Outline of the Disease.

As observed here, the disease presented certain characteristic features, viz. :

(1) Suddenness of onset.
(2) Severity of prostration.
(3) Constant involvement of the respiratory tract.
(4) High fever.
(5) Relatively slow pulse.
(6) Danger of rapid development of fatal complications.
(7) Frequency of psychical disturbance.
(8) Tendency to relapse.

V. Clinical Features of the Disease.

A. *Mode of Onset.*

This was always rapid, often sudden. Some men complained of malaise for several days before the severity of their symptoms com-

pelled them to come to hospital ; such cases on investigation were found to have been either originally mild cases which had developed complications or to be relapses. When treatment was sought early the onset was always described as sudden, with severe frontal headache, sometimes vomiting, fainting, usually with severe prostration, and often with shivering. We were impressed by the frequency with which patients coming under treatment late developed the disease in a severe form.

B. *Temperature.*

In uncomplicated cases the temperature reached its highest level during the first forty-eight hours. It remained at this level with remissions of 1° to 2° for twenty-four to forty-eight hours and fell by lysis with steep peaks reaching normal about the fifth day. Relapses two or three days later of slighter severity and shorter duration were not uncommon ; they recalled the intermittent pyrexia of trench fever. The original fall of temperature in a minority of the cases was by crisis.

C. *The Pulse.*

Relative slowness of the pulse was a striking and common feature. This lack of correspondence between the pulse and temperature curves was seen while the fever was at its height but before serious complications became manifest. As a signal of their imminence or onset a sudden rise in the pulse-rate was of great significance.

D. *Alimentary System.*

Tongue. In the majority of cases the tongue presented the appearance usually associated with a febrile disease, with the usual thick dry fur while the fever was maintained, and cleaning in the usual way when defervescence was established. Frequently, however, a peculiar mauve tint was seen on the dorsum and under-surface associated with a similar coloration of the fauces and lips. This appearance suggested a severe type of case : it was seen typically in ' toxaemic ' cases, and its appearance during the course of the disease was of ill omen. A return to normal colour of the tongue was an early sign of convalescence.

Stomach. Gastric disturbance was very common. Vomiting in the early stages has been seen frequently ; it usually ceased during the first forty-eight hours in the absence of complications or the excessive use of stimulating expectorants. Intractable vomiting persisting for several days was not uncommon in severe cases and its persistence after the first two days was regarded as a danger-signal. Haematemesis was not seen.

Bowels. Diarrhoea, often associated with vomiting, was common in the first forty-eight hours. During convalescence lienteric diarrhoea occasionally developed. Melaena occurred in three patients ; in one of these the quantity exceeded a pint ; in all it arose between the seventh and tenth days in cases of great severity but which ultimately recovered completely. Tympanites was not uncommon.

Liver. A mild degree of jaundice was seen in a few cases ; it

never lasted more than seven days. The cases were slight and recovered quickly. Tenderness over the liver was not complained of.

Spleen. No enlargement was detected. Pain in the splenic region was occasionally complained of, but no local physical signs could be found to explain its origin. Post-mortem examination occasionally revealed the presence of slight recent splenic enlargement.

E. *Respiratory System.*

Some degree of involvement of the respiratory tract was constant.

Sore throat at the onset was a very common complaint; no abnormality beyond redness of the pharynx with occasional oedema of the fauces was apparent at this stage.

Coryza and '*cold in the head*' very rarely occurred.

Epistaxis has been very common: usually only one nostril was involved: the flow was sometimes considerable and recurred on slight irritation: it was most common about the fifth day of illness; if occurring later in a case apparently progressing well it seemed to be an indication of commencing relapse or the development of a more serious phase.

Substernal pain varying from a mild soreness to acute pain was almost invariable; in association with this discomfort tender spots were commonly found in the skin over the first and second intercostal spaces.

Chest pain on breathing was not a feature of the uncomplicated cases, but was sometimes one of the earliest signs of pulmonary complication.

Cough. All these patients had a cough. In the early stages it was dry, 'tickling', and rapidly becoming painful. As the disease progressed there was a tendency for the cough to become paroxysmal. In the final stages of a 'pneumonia' case it sometimes ceased altogether.

Sputum. Much could be learnt of the progress of the case from an examination of the sputum. In the first stages it was scanty, clear, white, viscid. Later it became abundant, frothy, liquid, and often blood-stained. When pulmonary complications supervened its characters altered accordingly.

Haemoptysis was common in cases of moderate severity. It was bright, streaky, usually scanty, but in a few cases profuse. It was most common between the fourth and seventh days of illness. Its occurrence later with commencing pulmonary involvement was of serious significance.

Respiration-rate in uncomplicated cases was very little altered.

Aphonia was common, sometimes persisting throughout the course of the disease. It occasionally developed late or during convalescence.

Physical signs in uncomplicated cases were very slight. Movement was unimpaired, vocal fremitus unaltered. Breath sounds were weak in certain areas, usually over one lower lobe, and moist inspiratory crepitations were always to be found: low-pitched rhonchi were common, especially in the axillary region.

(The signs of pulmonary complication are discussed under that heading.)

F. *Circulatory System.*

Blood-picture. Slight leucopaenia with a striking decrease of eosinophile cells was the rule.

Blood-pressure. Little change was detected: a tendency to reduction of 'pulse-pressure' was noted in a few cases. No prognostic significance could be attached to blood-pressure readings. Dicrotism was not noticeable.

Pulse frequency. A striking feature has been relative slowness of the pulse during the course of the disease: a pulse-rate of 80–90 with a temperature of 102°–104° has not been uncommon. With the onset of serious complications a rapid rise in the pulse-rate has been an important and common feature.

Pulse rhythm. Arrhythmia during the height of the disease has not been noted. In the late stages of fatal cases intermittency has been common. During convalescence rhythmic irregularity associated with respiratory movements has often been found.

Heart. Evidence of myocardial distress, as shown by praecordial pain, dilatation, and alteration of the heart-sounds, was found only in cases presenting toxaemia or pulmonary complications.

Pericardial effusion was commonly found at post-mortem: it was never sufficiently large to give rise to definite signs during life.

No case of *Endocarditis* occurred in our series.

Cyanosis. A peculiar violaceous tint of lips and tongue has already been mentioned; spectroscopic examination of the blood from one of these cases revealed no abnormal absorption-bands. This tinting was most common in toxaemic cases, but was not entirely confined to those of great severity.

Thrombosis and *Embolism* have not been seen.

Haemorrhage. The disease was associated with a haemorrhagic tendency. No part of the body was exempt. Epistaxis and haemoptysis were very common; melaena was not rare, intramuscular haemorrhages were occasionally seen; petechial rashes occurred; petechiae on lungs and pericardium were found in most of the fatal cases; large haemorrhagic areas in the lung were common; blood cells were frequently present in the urine.

G. *Renal System.*

One case presented all the classical signs and symptoms of acute nephritis at the onset. The renal condition cleared up in ten days and, although the case ran a prolonged course, did not recur.

Albuminuria and the presence of a few renal cells and blood corpuscles have been common in the febrile stage of the disease, but renal symptoms have been absent.

H. *Nervous System.*

The chief nervous manifestations have been psychical. Profound mental inertia with intense physical prostration has been an early feature in many cases. Delirium has been very common: it has usually been worse at night. In its most common form it has been sudden in its onset, brief in its duration, sudden in its relief, and

frequent in its recurrence. It has varied from mere confusion of ideas through all grades of intensity up to maniacal excitement. A common feature of the illusions has been their pleasant nature: many of the severest cases have enjoyed a state of complacency or sense of well-being which was entirely out of keeping with the seriousness of their condition.

Depression has been substituted for this mental exaltation in a few cases throughout the course of the disease and it has been common during convalescence; in a few instances this depression has merged into melancholia.

Sleeplessness has been a very common and very obstinate symptom.

Sensory and Motor changes have not been observed, with the exception of one patient in whom a transient brachial monoplegia with aphasia developed: no explanatory signs were found in the brain *post mortem*.

I. *The Skin.*

Colour. Bright flushing of the cheeks was common at the commencement of the disease. The violaceous or heliotrope tint of the lips, which has already been referred to, sometimes was seen also upon the skin of the cheeks and neck.

Sweating has been a very striking feature; it has occurred copiously in cases from whom all drugs had been withheld. Profuse spontaneous sweating seemed to be an indication that the disease was about to be successfully overcome.

Rashes. Herpes of the lips has not been common: it was seen chiefly in the presence of severe pulmonary complications.

Urticaria was seen occasionally; it was widespread and the wheals were of large size.

Sudamina were quite common.

Petechial rashes occurred in three cases; two of these were fatal, the third made a slow but complete recovery. In one case the rash was very profuse and covered the whole of the dorsal aspect of the trunk and limbs; it spread on to the flanks but did not involve the face or anterior surface of the trunk. This patient died on the fifth day of illness with severe pulmonary lesions.

J. *Muscles.*

Pain in the large muscles has been a constant symptom in the early stages: warmth has given relief: movement has increased it. Pain and rigidity of the abdominal muscles has occasionally been so great as to suggest 'an acute abdomen'. Haemorrhage into the rectus abdominis was obvious in two out of our sixty-two post-mortem cases.

K. *Subcutaneous Emphysema.*

One case has occurred in which spontaneous surgical emphysema spread from the neck to the groin. The case was fatal, but no perforation in the air passages was discovered. In three other cases mediastinal emphysema was discovered at autopsy.

VI. Complications or Sequelae.

Two forms call for notice :

(A) Toxaemic.

(B) Pulmonary.

Both have been very serious and between them they have accounted for all our fatal cases.

A. *Toxaemic Complications.*

As a rarity the case has sometimes shown profound toxaemia from the commencement. Our most rapidly fatal case died on the third day of his illness. More frequently the evidence of severe intoxication has not appeared till the third or fourth day. Certain signs and symptoms seemed to be of grave significance, viz. :

(1) Early cyanosis.
(2) Early delirium.
(3) Sudden rise in pulse-rate.
(4) Late onset or persistence of vomiting.
(5) Epistaxis commencing after the fifth day.
(6) Obstinate constipation.

The mortality among these patients has been high, death usually occurring between the third and ninth days. Reaction to treatment has been disappointing. Early venesection (30 ounces) seemed to do good in a few cases ; if delayed beyond forty-eight hours after the appearance of grave symptoms it was useless.

Signs of commencing recovery were :

(1) A fall in the pulse-rate.
(2) Decrease of delirium.
(3) Cleaning of the tongue.
(4) Copious sweating with a fall of pulse-rate.

Blood-pressure readings gave no clue to prognosis in these cases.

B. *Pulmonary Complications.*

Some degree of trachitis was found in every case. The pulmonary complications which arose were :

(1) ' Oedema '.
(2) Broncho-pneumonia.
(3) Pulmonary haemorrhage.
(4) Pleural effusion.
(5) Bronchiectasis or abscess of lung.

The onset of lung-changes were indicated by :

(1) Alteration in the character of the sputum.
(2) Increase in the respiration-rate.
(3) Pain in breathing.
(4) Diminished respiratory movement.
(5) Diminution of air-entry.

When the complicating condition was well established the diagnosis seldom gave rise to difficulty except in the case of massive ' oedema ' or ' gelatinization ' of the lung, which was sometimes confused with pleural effusion.

Here the early or warning signs only are discussed.

The Sputum. Serious significance was attached to the following changes in the sputum :

(1) Great increase in quantity with the appearance of abundant liquid froth.

(2) Pink staining of the frothy sputum.

(3) Appearance of abundant pellets of thick, curdy muco-pus.

Rapid increase in the respiration-rate was sometimes the first indication of serious pulmonary involvement.

Pain on breathing—probably pleuritic in origin—occasionally gave the first sign.

Diminution of respiratory movement was found to be an important early sign in many cases.

Diminution of air-entry was found to be second in importance only to changes in the sputum as an indication of commencing pulmonary change. Temporary weakening of the respiratory murmur over certain areas of the lung, especially at the base, was very common at an early stage of even mild cases of influenza, but any extension of these quiet areas was found to be an important sign of lung-involvement.

' *Oedema of the lung.*' The macroscopic and microscopic characters of this condition are described elsewhere. Clinically it was found to be local or general : sometimes the upper lobes only were involved ; more often the condition was present in other parts of the lung as well. The physical signs associated with it were diminished movement, impaired percussion-note, decreased fremitus, weak breath-sounds, and abundant fine and medium inspiratory and expiratory râles. A few instances occurred in which the dullness was so great and the respiratory sounds so muffled that the presence of a considerable effusion was erroneously suspected.

The onset of this condition was sometimes within the first twenty-four hours ; more often it developed suddenly about the third or fourth day. It was not associated with oedema elsewhere, and there was nothing to suggest that it was cardiac or renal in origin. It seemed probable that the condition was a direct pulmonary manifestation of the action of the ' influenzal ' agent ; it did not appear comparable to the oedema of the lung associated with renal or cardiac disease.

Consolidation of the lung was common ; it was always lobular in origin, though often massive in its distribution. No case of true croupous lobar consolidation occurred in our series.

Pleural effusion was very common. Usually moderate in amount, it showed a great tendency to recur after aspiration. Empyema was common, though in many instances the purulent nature of the effusion was not suggested by the character of the temperature chart. It was found necessary to explore every case of pleural effusion, and a surprising number of unsuspected empyemata were thus revealed.

Nervous sequelae were occasionally observed. Depression was common.

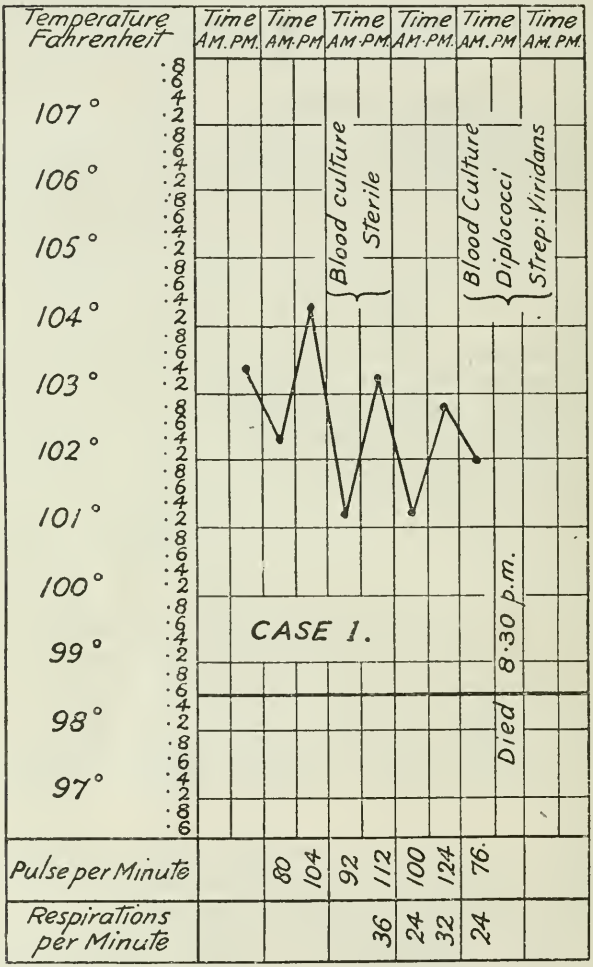
In one case very severe double nerve-deafness persisted for several weeks.

Case Records.

Case I. Ra.

Age 22. Onset Oct. 23. Admitted to hospital Oct. 25. Died Oct. 28 (6th day).

Oct. 25. Cyanosed. Rhonchi and râles over both lower lobes. T. 102°–104·2°. P. 104–90. Blood culture sterile. Throat swab—*B. influenzae*, *S. viridans*.



Oct. 27. Extension of signs to right upper lobe. T. 101·2°–102·8°. P. 100–124. R. 24–32.

Oct. 28. Moribund. Blood culture, diplococci and *S. viridans*.

Post mortem.

Epiglottis. Inflamed.

Aryteno epiglottidean folds. Oedematous.

Larynx. Intensely inflamed.

Trachea. Intensely inflamed.

Pleura. ℥x turbid semipurulent fluid in left sac. Haemorrhages on diaphragmatic surface of visceral pleura and anterior surface of lungs.

Right lung. Lower lobe and part of middle lobe red, homogeneous, gela-

tinous. Tortoise-shell appearance of surface. Upper lobe solid, granular, pus in bronchi.

Left lung. Upper lobe aerated. Lower lobe pouring fluid on section.

Liver. Large, pale, greasy patches on surface and in substance.

Spleen. Normal.

Suprarenals. Normal.

Kidneys. Normal.

Cultures post mortem.

Lung. *B. influenzae* and *S. viridans.*

Bronchial fluid. *B. influenzae* and *S. viridans.*

Heart blood. *S. viridans.*

Pericardial fluid. *S. viridans.*

Special Features. A case fatal on 6th day, presenting high, falling temperature, relatively slow but quickening pulse, little respiratory distress, great involvement of lung.

Microscopic appearance.

Right lung. Lower lobe. Section shows intense congestion. The alveoli are filled with fibrinous exudate, which shows a varying amount of leucocytic invasion. Around the smaller bronchi leucocytic accumulation is marked.

Upper lobe. Shows great congestion. The alveoli contain a granular deposit with very few leucocytes.

Case II. Mu.

Age 27. Onset Oct. 23. Admitted Oct. 25. Recovered.

On admission flushed, T. 104·6°, P. 100, R. 28. Impaired percussion note and air-entry at both bases. Slight friction right lower axilla.

5th day of illness. Friction ceased. Air entry still impaired. Sputum clear, viscid. T. 102°–101·4°. R. 30.

6th day of illness. Temperature normal. P. 72. R. 20.

7th–11th day. Temperature subnormal. General condition, no distress. Cough persisting. Sputum mucopurulent.

12th day. Relapse pyrexia to 102·4°. P. 92. No distress and no fresh lung-signs.

13th day. Temperature fell to normal during the day and remained subnormal till 18th day.

18th day. Transient rise of temperature to 101°.

Subsequent course: steady convalescence.

Summary. Uncomplicated case. Relative slowness of pulse during course and convalescence. Two pyrexial relapses. Ultimate complete recovery.

Throat swab. 4th day. *B. influenzae* and meningococci (?). No pneumococci or streptococci.

Naso-pharyngeal swab. 4th day. *B. influenzae*, meningococci (?). No streptococci or pneumococci.

Case III. Pe.

Age 27. Onset Oct. 22. Admitted Oct. 25. Died 16th day.

On admission (4th day). T. 103·2°. P. 100. R. 42. Signs of bronchitis general, but especially evident in right lower and left upper lobes. Sputum frothy. No signs of consolidation. Throat swab, *S. salivarius*, *S. viridans.*

6th day. Signs more extensive. Sputum more abundant and very watery.

8th day. Increasing respiratory distress. Cyanosis. Temperature falling to 100°. Pulse-rate raised to 116. Sputum blood-stained, *B. influenzae*, a few *S. viridans.*

10th day. Sputum purulent. Coarse crepitations general. Impaired movement of right chest and bronchial breathing over right lower lobe.

10th–16th day. Steady increase in severity of pulmonary symptoms, with extension of broncho-pneumonic patches, falling temperature with rising respiration-rate.

Bacteriology.

Post mortem. Pericardial fluid, negative. Pleuritic exudate, haemolytic streptococci and *S. viridans.* Fluid from bronchi, *B. influenzae* in large numbers and numerous *S. viridans.* Tracheal fluid, a few colonies of haemolytic streptococci.

Sputum. B. influenzae (profuse growth), *S. viridans*, *M. catarrhalis.*

Naso-pharyngeal swab. S. viridans, *S. salivarius.*

Post mortem.

Pericardial effusion. 6 ounces clear fluid (sterile).

Heart. Thin walled and flabby.

Larynx. Inflamed.

Trachea. Much inflamed ; containing milky, frothy fluid.

Pleura. Gelatinous lymph on surface of right lower lobe.

Right lung. Surface haemorrhages. Haemorrhagic infaret (?) in upper lobe. Appearance of grey hepatisation in greater part of lower lobe and small part of middle lobe.

Left lung. Surface haemorrhages. Upper lobe engorged and pouring fluid on section. Lower lobe capillary broncho-pneumonia with multiple 'pock-mark' abscesses.

Summary of Case. Fatal case with lung complications present on the 4th day. Lung condition increasing in extent and severity. Haemorrhagic process well marked.

Microscopic appearance.

Left lower lobe. Shows abscess formation with complete solution of bronchial wall and cavitation due to formation of pus. Great engorgement of whole section ; remaining alveoli are filled with fibrin and leucocytes with a varying admixture of red blood corpuscles.

Case IV. Wu.

Age 34. Onset Oct. 22. Admitted Oct. 24. Complete recovery.

On admission. T. 103. P. 90. R. 24.

3rd day. Weak breath sounds and few crepitations at left base only.

4th day. T. 100·8°–102·4°. Air entry good at both bases. Few crepitations on inspiration R. and L. Sputum scanty, viscid, white.

Naso-pharyngeal swab. B. influenzae. Gram-negative diplococci, probably meningococci. No growth on plain agar.

5th day. Lung signs clearing. Temperature normal. R. 20. P. 70.

7th day. No signs in lungs. No rise of temperature.

Summary. An uncomplicated case, rapid fall of temperature. No relapse.

Case V. Wa.

Age 19. Onset Oct. 21. Admitted Oct. 25. Recovery.

On admission (5th day). Fauces injected. Lumbar pain. T. 103·6°. P. 104. R. 44. Substernal pain. Inspiratory crepitations right upper lobe and upper part of left lower lobe. Pink sputum.

6th day. Impaired air entry and percussion-note both lungs. Many crepitations. No bronchial breathing.

Naso-pharyngeal swab. Pneumococci, *B. influenzae*, haemolytic streptococcus.

8th day. Definite tubular breathing at apex of right lower lobe. Impaired note and many moist sounds at both bases. Sputum muco-purulent.

10th day. No tubular breathing. Coarse crepitations both lower lobes. Fine crepitations both upper lobes. Sputum muco-purulent.

12th day. Signs clearing.

15th day. Aphonia.

19th day. Voice returned, convalescence established.

Clinical Summary. Severe case in young subject with pulmonary complications. Rapid respiration and early haemoptysis. Relatively slow pulse through out. No cyanosis. Steady convalescence and complete recovery.

Case VI. Gr.

Age 38. Onset Oct. 26. Admitted Oct. 28. Recovery.

On admission. Much cough, scanty sputum.

3rd day. Moist sounds at left base, air entry poor. T. 103°. P. 108. R. 26.

Naso-pharyngeal swab. B. influenzae, staphylococci, and a gram-negative diplococcus, *M. catarrhalis.*

5th day. Little sputum, becoming muco-purulent. More moist sounds in chest. Air-entry good.

7th day. Temperature normal in morning. Practically no chest signs. Cough loose and decreasing.

9th day. Convalescence established.

Clinical Summary. A mild uncomplicated case ending in complete recovery.

Case VII. We.

Age 32. Onset Oct. 30. Admitted Oct. 30. Recovery.

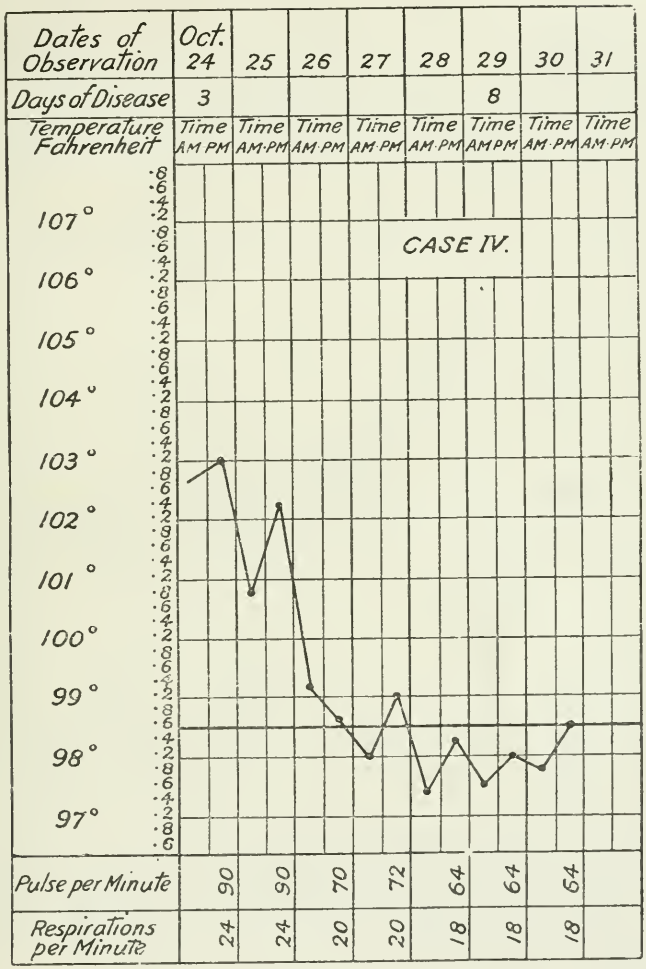
Onset sudden with shivering, faintness, pains all over. Slight dry cough. No chest signs.

Naso-pharyngeal swab. *B. influenzae*, Vincent's organisms, *S. viridans.*

3rd day. Still no sputum. Severe pains in muscles of thigh, and legs.

5th day. Relapse pyrexia. No chest signs.

Summary. A mild uncomplicated case seen from time of onset. Early relapse. Complete recovery.



Case VIII. Kl.

Age 21. Onset Oct. 31. Admitted Nov. 1. Recovery.

On admission. T. 104°. P. 72. R. 24.

2nd day. Scanty sputum. Coarse crepitations both bases, especially left.

Naso-pharyngeal swab. Haemolytic streptococcus. *B. influenzae.*

Sputum. *M. catarrhalis* and *S. viridans.*

4th day. Definite bronchial breathing left upper lobe. Many moist sounds left lower and right lower lobe. T. 104·2°. P. 72. R. 24.

6th day. Temperature falling. No bronchial breathing.

8th day. Temperature normal. Lung signs clearing.

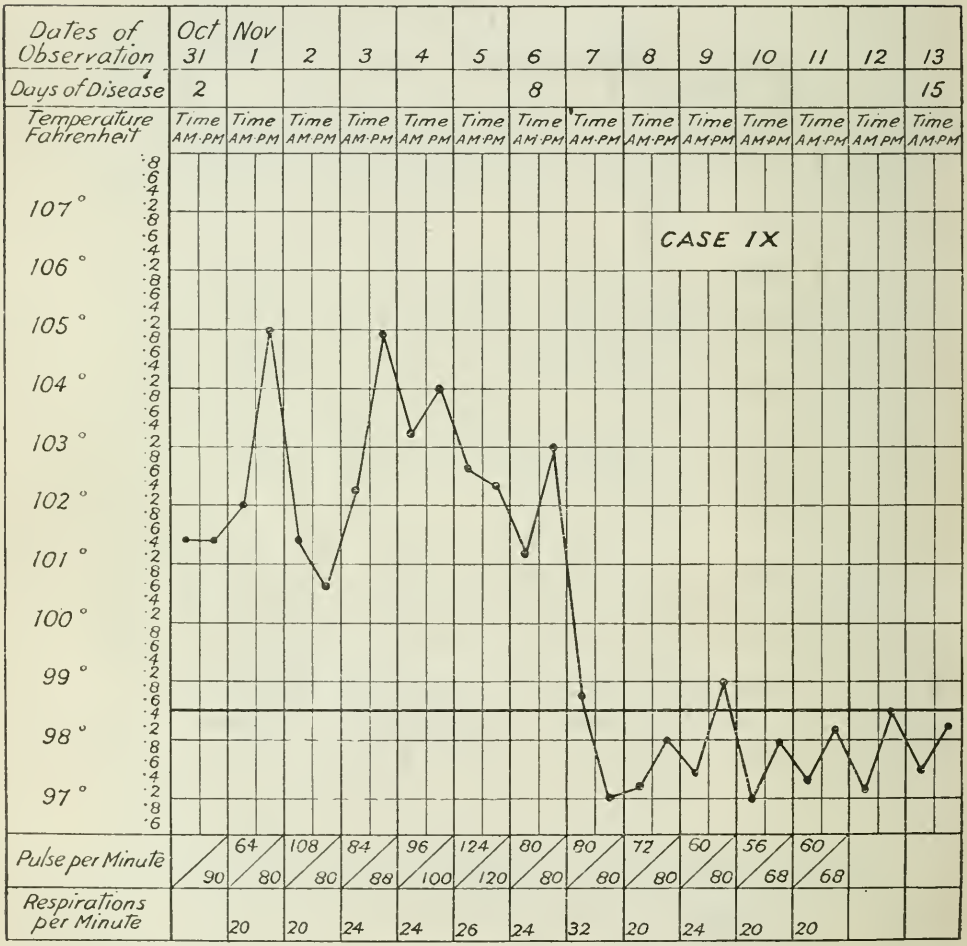
Clinical Summary. A case of moderate severity with definite lung complications. Pulse and respiration slow throughout. Rapid improvement of lung condition. Steady convalescence.

CASE IX. Ri.

Age 20. Onset Oct. 29. Admitted Oct. 31. Recovery.

Onset, sudden with shivering, headache, cough, and limb-pains.

3rd day. T. 105°. P. 80. R. 20. Coarse crepitations left base. Sputum viscid, white.



Throat swab. B. influenzae. M. catarrhalis, a few pneumococci (?).

Sputum. B. influenzae, a very few Diplococci.

5th day. T. 105°. P. 88. R. 24. Crepitations in both lungs. No tubular breathing. Sputum more liquid.

7th day. Delirious (mild). Sputum purulent (no blood-staining). Temperature falling. Pulse rising.

8th day. Mentally clear. P. 80. R. 24. Temperature falling.

10th day. Temperature subnormal. Few moist sounds only in lungs.

Clinical Summary. Severe case with mild pulmonary involvement. Remarkable absence of pulse or respiration disturbance. Complete recovery.

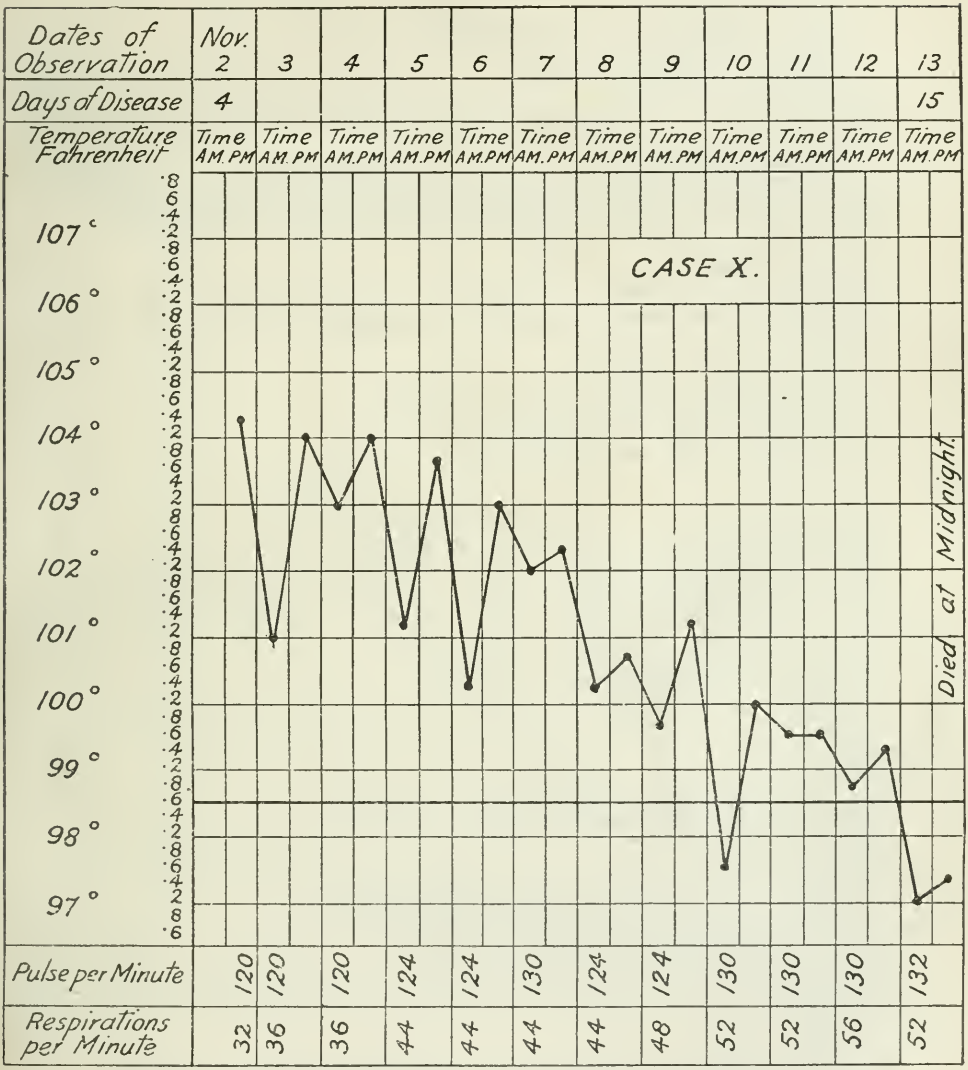
Case X. Be.

Age 23. Onset Oct. 30. Admitted Nov. 2. Died 16th day.

Onset with rigor, cough, and general pains.

5th day. Cyanosed, delirious. Consolidation right upper lobe. Crepitations and poor air-entry over left lower lobe. T. 104·2°. P. 120. R. 32.

7th day. No change.


Dates of Observation
Nov. 2 3 4 5 6 7 8 9 10 11 12 13
Days of Disease
4 15
Temperature Fahrenheit
Time AM. PM
107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97°
CASE X.
Died at Midnight.
Pulse per Minute
120 120 120 124 124 130 124 124 130 130 130 132
Respirations per Minute
32 36 36 44 44 44 44 48 52 52 56 52

9th day. Consolidation left lower lobe. No change in right lung.

11th day. More distressed. Temperature falling. Respiration rising.

13th day. More distressed. Cough ceased.

16th day. Died.

Post mortem.

Pharynx. Retronasal abscess.

Trachea. Mild inflammation.

Tracheal glands. Enlarged.

Pericardium. 10 oz. of clear effusion.
Heart. Normal.
Pleura. Surface haemorrhages, fibrin on lung surfaces.
Right lung. Upper lobe, grey, streaming fluid on section, breaking down in parts, pus in bronchioles. Middle lobe clear. Lower lobe some surface haemorrhages.
Left lung. Upper lobe, greyish pink, mottled, granular, moist. Lower lobe, patchy consolidation.
Liver. Moderately fatty, much engorged.
Spleen. Normal.
Kidneys. Pale, swelling of cortex.
Suprarenals. Healthy.
Clinical Summary. A fatal case in a young subject, early severe involvement of lung.
Microscopic Appearance.
Left lower lobe. Section shows almost universal consolidation with intense engorgement and destruction of bronchial mucous membrane in smaller bronchi. Leucocytic infiltration of fibrinous exudate is present through the whole section. No abscess formation.
Pleura. Shows fibrinous pleurisy.
Bacteriology (post mortem).
From retronasal abscess. *B. influenzae* in large numbers and a few *S. viridans.*
Pericardial fluid. Negative.
Heart's blood. Negative.
Bronchial fluid. *S. viridans* and *B. influenzae.*
Tracheal scraping. *B. influenzae* only.
Lung culture. An occasional diplococcus.
Pleural pus.

Case XI. Ho.

Age 32. Onset Nov. 1. Admitted Nov. 2. Recovery.
Onset sudden. General pains.
3rd day. Cough, little frothy sputum. T. 101·4°. P. 84. R. 20. Few scattered moist sounds in chest.
4th day. Sputum. *B. influenzae* and *S. viridans.*
5th day. Chest signs clearing.
8th day. Temperature normal. Chest clear.
Clinical Summary. A very mild uncomplicated case with complete recovery. No relapse.

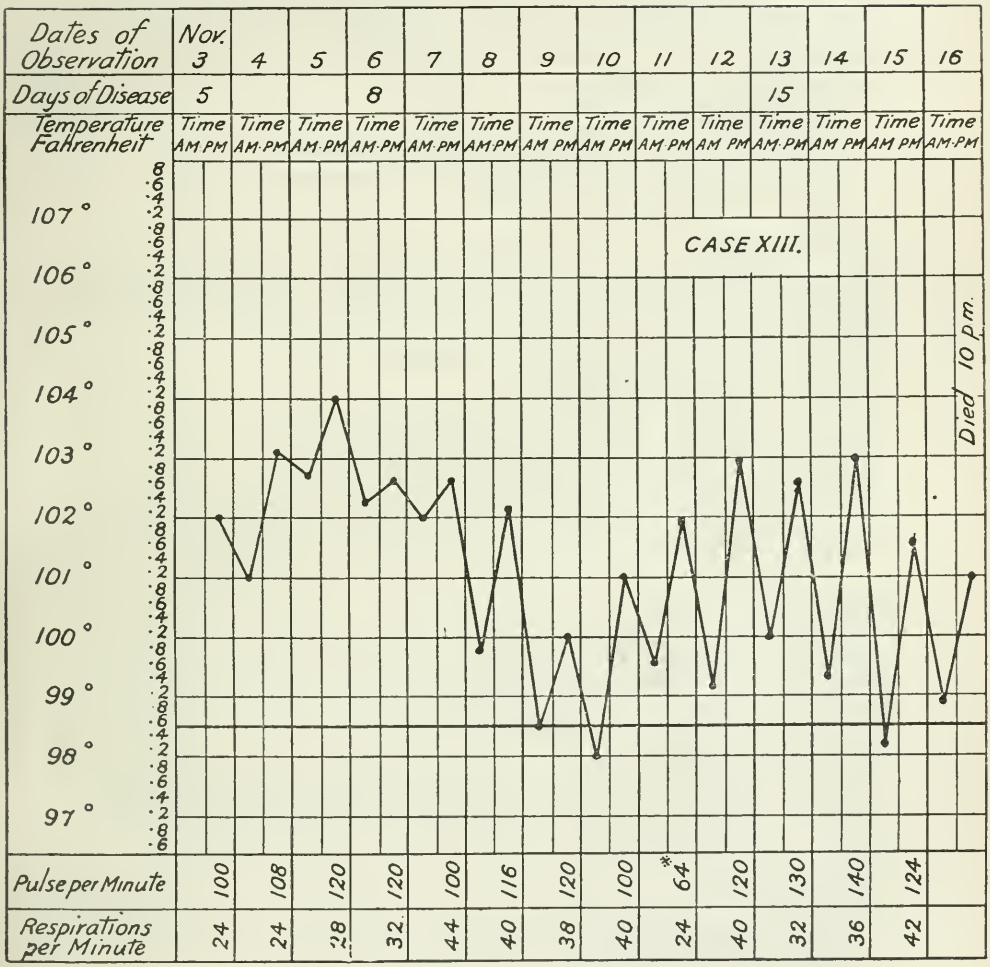
Case XII. Bu.

Age 28. Onset Nov. 3. Admitted Nov. 3. Recovery.
Onset with shivering, general limb-pains.
On admission. T. 103°. P. 80. Dry cough: scanty viscid sputum. No signs in chest.
2nd day. T. 100°. P. 60. R. 20. No chest signs.
Sputum. B. influenzae, M. catarrhalis, and *S. viridans.*
3rd day. Temperature normal. No discomfort.
5th day. Relapse pyrexia: shin pains.
Clinical Summary. A very mild case of influenza or more probably a case of trench fever.

Case XIII. Me.

Age 27. Onset Oct. 30. Admitted Nov. 3. Died 18th day.
On admission (5th day). T. 102°. P. 100. R. 24. Substernal pain. No distress. Crepitations right and left base and right submammary. Sputum scanty, viscid.
7th day. Moist sounds general.
8th day. Respiration hurried at times.
10th day. Much distressed. Sputum abundant, frothy.
12th day. Blood in sputum: creamy pus.
13th day. Chest full of moist sounds, dullness both lower lobes.

15th day. Cyanosis and great distress.
16th day. Cough ceased.
18th day. Died.
Post mortem.
Larynx. Moderate inflammation.
Trachea. Moderate inflammation. Creamy pus in trachea, no froth, no blood.
Pericardium. 10 oz. of fluid.



Heart. Dilatation of right chambers.
Pleura. Right obliterated by old adhesions. Left, 1–2 oz. of cloudy fluid.
Right Lung. Studded throughout with small patches of broncho-pneumonia. Small abscess cavity in lower lobe.
Left Lung. Upper lobe aerated, but pouring fluid on section. Lower lobe many patches of broncho-pneumonia.
Liver. Fatty.
Spleen. Small and soft.
Clinical Summary. A fatal case with early pulmonary complications. Transient improvement followed by extension of involvement of lung.

Microscopic Appearance.

Left lower lobe. Section 1 shows universal consolidation and great engorgement with definite small haemorrhages into alveoli scattered through section. Leucocytic invasion of fibrinous exudate, though apparent through section, is more marked around the smaller bronchi, some of which show destruction of mucous lining.

Section 2 shows patchy consolidation in which the intensity of the injection is concentrated round the smaller bronchi. In some mucous membrane has been destroyed, and in others both mucous membrane and fibrous wall are in the process of destruction. Leucocytic accumulation, marked at these points, diminishes as one passes to the parenchyma of lung, and, finally, on the fringe of a bronchopneumonic area, alveoli are found containing fibrin only.

Bacteriology.

Heart's blood. Negative.
Pericardial fluid. Negative.
Bronchial fluid. *B. influenzae* (numerous), *S. viridans.*
Tracheal scraping. *B. influenzae* (profuse), *S. viridans.*
Pleural exudate. *B. influenzae* (profuse), *S. haemolyticus*, *S. viridans.*
Lung. *B. influenzae* and *S. viridans.*

Case XIV. Fa.

Age 26. Onset Nov. 3. Admitted Nov. 3. Recovery. Onset with shivering, headache, substernal pain and aching limbs. No signs in chest. T. 102·4°. P. 80. R. 20.

3rd day. Few moist sounds in chest. Scanty viscid sputum.
6th day. Epistaxis. Cough looser.
7th day. Sputum frothy mucus.
8th day. Epistaxis ceased. Temperature normal.
10th day. Sputum slightly muco-purulent.
12th day. More cough, scattered moist sounds in chest.
14th day. Convalescence established.

Clinical Summary. A case of moderate severity, uncomplicated, ending in complete recovery without relapse.

Sputum. Haemolytic streptococcus, *S. pyogenes*, no *B. influenzae.*

Case XV. Wh.

Age 20. Onset Nov. 7. Admitted Nov. 8. Died 11th day. Onset sudden with shivering, headache, and vomiting.

2nd day. Sputum frothy, mucoid, white, unstained. Crepitations over left upper lobe. Bases clear. T. 103·8°. P. 100.

3rd day. Vomiting continues. Sputum mucopurulent. Impaired note and air-entry at right base.

5th day. Vomiting continues. Sputum pink, frothy.

7th day. Vomiting continues. Sputum rusty. Consolidation, right lower lobe.

8th day. Fall of temperature. Greater distress. Abundant liquid stained sputum. Vomiting ceased.

10th day. *In extremis.* Irregular pulse.

11th day. Died.

Post Mortem.

Larynx. Not inflamed.
Trachea. Slightly inflamed, containing brown frothy fluid.
Tracheal Glands. Swollen.
Pleura. Recent dry pleurisy over left lower lobe.
Right Lung. Deep area of consolidation in upper lobe. Middle and lower lobes not involved.
Left Lung. Massive consolidated areas in lower and part of upper lobes.
Pericardium and Heart. Normal.
Liver. Diffuse and localized pallor in left lobe.
Spleen. Soft and swollen.
Kidney. Swelling of cortex, with blurring of structure.

Clinical Summary. A fatal case in a young subject with obstinate vomiting, some haemoptysis, and severe pulmonary complications.

Microscopic Appearance.

Left lower lobe. Section shows great engorgement and almost universal consolidation. Small scattered areas of haemorrhage are present. Leucocytic invasion of consolidated area is universal, being more marked at the sites of the smaller bronchi.

High power. Shows cellular accumulation to consist of (1) polymorphonuclear leucocytes; (2) mono-nuclear cells (small), probably young filioblasts and lymphocytes; (3) mono-nuclear cells (large), probably catarrhal cells derived from cells lining alveoli.

Bacteriology.

Heart's blood. Negative.

Pericardial fluid. Negative.

Bronchial fluid. *B. influenzae* and *S. viridans.*

Tracheal Scraping. Gram-negative diplococci do not grow on plain agar, probably meningococci.

Pleural exudate. *B. influenzae*, a few staphylococci.

Lung. *S. viridans.*

Tracheal fluid. Negative.

Case XVI. Pe.

Age 31 years. Onset Nov. 11. Admitted Nov. 13. Recovery. Onset with substernal pain and cough, backache and limb-pains. No shivering.

3rd day. T. 102. R. 22. P. 84. Many crepitations at left apex (this patient had previously been under observation as a case of suspected tuberculosis). Scattered rhonchi. Sputum white and frothy.

5th day. T. 100. P. 80. R. 24. Chest signs unchanged. Sputum mucopurulent.

6th day. T. normal. More moist sounds in chest.

8th day. Chest signs clearing.

10th day. Convalescence established.

12th day. No relapse. Still a few signs at left apex.

Clinical Summary. A mild case in a subject of slight chronic bronchitis, no complications, complete recovery without relapse.

Naso-pharyngeal swab (17.11.18). *B. influenzae, S. viridans.*

Case XVII. Gl.

Age 19. Onset Nov. 12. Admitted Nov. 16. Died 11th day.

On admission (5th day). T. 104·4°. P. 106. R. 40. Crepitations and impaired air-entry over upper part of right lower lobe. Sputum viscid, pink.

6th day. Left lower lobe solid. Many crepitations, left lower lobe. Sputum more fluid.

7th day. Delirious. Cyanozed. No sputum.

8th day. Great distress. T. falling. Cough ineffectual. Consolidation of left lower lobe.

9th day. Subcutaneous emphysema of neck.

11th day. Died.

Post mortem.

Subcutaneous emphysema of face, neck, and trunk.

Larynx. Acutely inflamed.

Trachea. Intensely inflamed with haemorrhagic areas and necrosis of mucosa.

Pleural sacs. Dry. Haemorrhages on lung-surfaces.

Right lung. Capillary broncho-pneumonia involving larger portion of all lobes.

Left lung. Upper lobe emphysematous. Lower lobe, massive broncho-pneumonia.

Heart and Pericardium. Normal.

Liver. Many fatty areas.

Spleen. Soft.

Kidneys. Cortex pale, swollen, structure blurred.

Suprarenals. Healthy.

Clinical Summary. A fatal case in a young subject, pulmonary complications arising early. Very intense tracheal inflammation. Extensive subcutaneous emphysema.

Naso-pharyngeal swab (19.11.18). *B. influenzae, S. viridans.*

Histology. Left lung, lower lobe. Section shows almost universal consolidation and great engorgement. Leucocytic penetration and infiltration of the inflammatory exudate is advanced. Bronchi in section are filled with leucocytes and desquamated epithelial cells. Destruction of the ciliated bronchial mucous membrane is marked. There is no abscess formation. Great destruction of interalveolar septa is present, section being almost unrecognizable as lung tissue.

Case XVIII. Ca.

Age 22. Onset Nov. 22. Admitted Nov. 22. Recovery. Onset with substernal pain, shivering. T. 102·4°. P. 112. R. 20.

1st day. Air-entry unimpaired. Few crepitations left base. Dry cough, viscid sputum.

2nd day. T. falling. Signs unaltered.

4th day. T. 99·6. More cough, sputum scanty, mucopurulent. No chest signs.

6th day. T. normal.

8th day. Relapse. T. 101·4°. P. 104. R. 38. No fresh signs in chest.

10th day. T. subnormal. No complaints. Cough practically ceased.

Clinical Summary. Mild uncomplicated case in young subject. One relapse followed by complete recovery.

Naso-pharyngeal swab (23.11.18). *B. influenzae, S. viridans.*

Case XIX. Ca.

Age 28. Onset Nov. 22. Admitted Nov. 24. Recovery.

On admission, T. 104. P. 84. R. 20.

3rd day. Dry cough, very scanty sputum. Substernal pain. No signs in chest.

5th day. T. 102°. Cough looser. Few moist signs at left base.

7th day. T. 99°. Chest clear.

8th day. T. normal. Cough much less.

Clinical Summary. Mild uncomplicated case. Complete recovery without relapse.

Bacteriology. No examination.

Case XX. Pr.

Age 39. Onset Nov. 29. Admitted Nov. 29. Recovery.

1st day. Shivering, general pains, headache, vomiting. Crepitations and prolonged expiratory murmur at both bases. Scanty viscid sputum.

3rd day. Vomiting ceased. Pain in limbs persists. Lung condition unaltered. Urine contains faint trace of albumen, no cells, no casts. T. 101·4°. P. 90. R. 24.

5th day. T. normal. No pain. Urine normal. Few moist sounds at bases only. Cough ' loose '.

7th day. Evening T. 99°. No complaint.

9th day. Convalescence established.

Clinical Summary. A mild short uncomplicated case in a middle-aged subject.

Bacteriology. No examination.

3 (*b*). THE MORBID ANATOMY OF INFLUENZA

BY

Major C. E. Sundell, R.A.M.C.

The following account is based upon the findings on post-mortem examination of sixty-two cases.

I. External Appearances.

Wasting has not been a striking feature.

Rash was present in two cases : it was profuse, petechial, macular : the face was not affected.

Subcutaneous emphysema was extensive in one case.

Oedema was not seen.

II. Muscles.

Interstitial haemorrhage into the rectus abdominis had occurred in two cases.

III. Respiratory System.

A. *Pharynx.*

Congestion was common, purple coloration was occasionally seen.

Retronasal abscess was present in one case.

B. *Larynx.*

Congestion was common, sometimes intense with purple discoloration.

Aryteno-epiglottidean folds were often oedematous.

C. *Trachea.*

Inflammation found in every case, often confined to region below fourth tracheal ring, sometimes intense : haemorrhagic areas and shallow necrosis of the mucosa seen occasionally.

Tracheal contents usually frothy fluid, often blood-stained.

Tracheal glands swollen, reddish purple, never suppurating.

Bronchial glands often swollen and engorged.

D. *Pleural Sacs.*

Frequently containing moderate effusion, clear with a little floating lymph. Haemothorax never seen.

Pleural surfaces : superficial haemorrhages were very common especially on the posterior surfaces of the lungs. Thin fibrinous pleurisy often seen over involved areas of the lung but strikingly less than that found over areas of pneumonic consolidation.

E. *Mediastinum.*

Emphysema of upper and anterior mediastinum was seen in three cases.

F. *Lungs.*

Very striking changes were found :

(*a*) ' Oedema ' ; (*b*) ' gelatinization ' ; (*c*) haemorrhage ; (*d*) broncho-pneumonia ; (*e*) abscess formation was seen in three cases which had died at an early stage.

(a) ' *Oedema* ' *of lung.* Distribution roughly lobar. The affected area is firm, heavy, crepitant, retains its shape, has a smooth surface often showing petechial haemorrhages : on section no consolidation is present ; the cut surface pours out fluid which is clear, slightly brownish and frothy. No pus can be squeezed from the bronchioles.

This type of lung occurs in early cases who have shown much frothy liquid sputum during life and in whom the affected area has given a flat note on percussion, air entry has been poor and many inspiratory and expiratory crepitations have been present.

(b) ' *Gelatinization* ' *of lung.* Distribution roughly lobar, both lungs usually involved, right middle lobe often free. Surface is smooth or thinly coated with fibrin. On section the lung is red, homogeneous, glassy ; it contains excess of fluid and is nearly airless.

The physical signs presented during life are similar to those of the ' oedema ' cases but the dullness is more marked, air entry is more impaired, and occasionally tubular breathing is audible.

(c) *Haemorrhage.* Haemorrhage into the lung substances has been common. The haemorrhagic areas are irregular in size and shape ; sometimes they are conical suggesting infarction. The condition is often associated with broncho-pneumonia, from which it cannot be differentiated during life.

(d) *Broncho-pneumonia* and capillary bronchitis are common in all grades in late cases. ' Miliary broncho-pneumonia ' was seen in four cases.

IV. Circulatory System.

A. *Pericardium.*

Moderate effusion (ʒx) was not rare. It was sometimes cloudy but never blood-stained.

Petechiae of the visceral and parietal surfaces were very common.

B. *Heart.*

Nothing abnormal was detected except flabbiness of heart-muscle and usually dilatation of r. chambers.

Valves and aorta were always normal.

V. Alimentary System.

A. *Liver.*

Pallor was very common. It was usually concentrated in patches on and near the surface, especially of the left lobe, but was often diffuse.

Associated with this in a few cases was a slight fibrosis.

B. *Spleen.*

The only abnormality detected was occasionally slight swelling. The organ was usually soft and engorged.

C. *Pancreas.*

Normal.

D. *Intestine.*

Slight injection of mucosa of colon was occasionally seen. No haemorrhagic areas were found. Intestinal lymphatic glands were normal.

E. *Peritoneum.*

Normal.

VI. Other Organs.

A. *Kidneys.*

Little change was noted other than that associated with a febrile illness. In a few cases marked pallor and swelling of the cortex with blurring of the structure suggested subacute nephritis.

B. *Suprarenals.*

No haemorrhages were seen in cortex or medulla.

C. *Brain.*

No abnormality was discovered on naked-eye examination of the brain or meninges.

3 (*c*). THE MORBID HISTOLOGY OF INFLUENZA

BY

CAPTAIN J. I. CONNOR, A.A.M.C.

THE material for this study was obtained from post-mortems on cases of influenza conducted by Major Sundell, R.A.M.C., whose description of the gross morbid anatomy appears elsewhere in this monograph.

Sections of tissue were fixed in 10 per cent. formalin solution, and the usual routine for paraffin sections was followed. As a general rule haematoxylin and eosin were used for staining, but variations were made where necessary for special examinations, i. e. fat, bacteria, capsules, &c.

I. LUNGS.

The histological examination of the lungs being of great importance is divided into five headings, as follows :

A. Areas of haemorrhage.
B. Areas of broncho-pneumonia.
C. Areas of oedematous pneumonia.
D. Areas of grey hepatization with multiple abscess formation.
E. Areas of consolidated lung ranging in colour from red to grey and usually ' dripping '.

A. *Areas of Haemorrhage.* (See Plates I and XI A).

The predominating factor is haemorrhage into the alveoli. Great engorgement of all the vessels is present. The majority of the alveoli are plugged with inflammatory exudate, many showing the reticulum of fibrin with a varying admixture of red blood corpuscles. In some areas these red blood corpuscles have undergone haemolysis and in others still retain their original shape. Occasionally a group of alveoli is seen filled with blood only and in many places rupture or solution of the inter-alveolar septa is apparent. The picture is one of acute haemorrhagic inflammation with toxic spoiling of the capillaries. Although cellular reaction is not marked at this stage, it is most evident in and around the bronchioles, many of which are filled with polymorphonuclear leucocytes and débris of desquamated ciliated epithelial cells. In some cases the mucous membrane is totally destroyed, leaving the fibrous walls exposed and even split by the cellular infiltration, with partial solution. The sub-bronchial lymphatic spaces are also infiltrated by leucocytes. Passing to the parenchyma of the lung, leucocytes (largely polymorphonuclears) are dotted sparingly through the mixture of haemorrhage and inflammatory exudate. Many large phagocytic mononuclear endothelial cells can be seen, some still attached to the alveolar walls, and some forming part of the imflammatory exudate filling the alveoli.

B. *Areas of Typical Broncho-pneumonia.* (See Plate XI B).

Under the low power patchy areas of inflammatory change are apparent and the infection is concentrated around the smaller bronchi. Stages in the process of their destruction can be seen.

(1) Desquamation of the mucous membrane with leucocytic accumulation in the lumen.

(2) Infiltration of the sub-mucous and fibrous layer.

(3) Gradual solution and splitting of the fibrous tissue of the wall.

The nucleii of ciliated cells are swollen and granular, and the surrounding alveoli, where evident, are filled with inflammatory cells. In many cases the small area of lung affected, and appearing as a white nodule at autopsy, is unrecognizable as lung tissue, consisting only of a mass of leucocytes, fibrin, catarrhal cells, and remnants of destroyed lung tissue.

Passing to the parenchyma of the lung, the alveoli are seen retaining their shape, and filled with inflammatory cells and fibrin; alveoli with fibrinous reticulum, or homogeneous albuminous exudate only, and finally empty alveoli somewhat distorted during fixation, with slight inflammatory change. The picture is one of patchy inflammation concentrated round the bronchioles with marked cellular reaction, and destruction of tissue but with little haemorrhage. Sections stained by Giemsa stain show that bacteria are most numerous in the leucocytic plug in the bronchioles and neighbouring tissues, becoming less frequent as the parenchyma is approached.

C. *Areas of Oedematous Pneumonia.* (See Plate XII A).

Lung section. There is no universal consolidation and destruction of tissue is not marked. Section on examination appears as an open network of interalveolar septa except those parts approximating the bronchioles. General engorgement is marked and groups of alveoli throughout the section are filled with red corpuscles. The bronchioles show marked damage with desquamation of the ciliated epithelium and partial solution of the fibrous wall. Leucocytic reaction is marked in and around these bronchioles, many being filled with a leucocytic plug. Approximate alveoli are also plugged with a mixture of inflammatory cells.

Passing to the parenchyma of the lung, capillary engorgement is marked. The phagocytic cells lining the alveoli are markedly active, showing increase in size and a tendency to become detached and to accumulate in the alveoli.

The majority of the alveoli contain only a few free endothelial cells, leucocytes, and granular débris, these alveoli being filled at autopsy with oedema fluid.

D. *Areas of Grey Hepatization and Abscess Formation.* (See Plate XII B).

Almost universal consolidation is present and cellular reaction is marked. Every alveolus, still recognizable as such, is filled with phagocytic macrophages from the alveolar walls, and smaller mononuclear cells. This cellular accumulation is marked in certain areas, identified as sites of smaller bronchi, by remnants of ciliated epithe-

lium and fibrous tissue of the wall. Tissue destruction in these areas is marked, and multiple abscess cavities are present. The surrounding lung tissue is not recognizable as such, being converted into a mass of inflammatory cells. The parenchyma of the lung shows some alveoli (usually grouped) filled with red blood corpuscles.

A fibrinous pleurisy is commonly seen with early organization of the fibrin.

E. *Areas of consolidated Lung of varying Colour.* (See Plate XIII).

The three sections already described are definite types seen during the epidemic, and every transition may be seen from one to the other, and a combination of all three in the same lung.

As a rule the acute cases, where early death has supervened, show a markedly haemorrhagic lung. Where death occurred later in the infection the usual change of colour, apparent in lobar pneumonia, is present. Grey hepatization, purulent infiltration, or multiple abscess formation alter the picture and always show a patchy distribution, in contradistinction to lobar pneumonia where an entire lobe or the whole of one or both lungs have suffered equally.

Sections stained for bacteria by Giemsa (Pasteur Institute), twenty-four hours' immersion, show the preponderance of diplococci in our sections, a pleomorphic diplo-streptococcus being very frequent (see Plates VI and VII).

A few bacilli suggestive of *B. influenzae* were seen, but not in quantity as reported by Muir (*B. M. J.*, January 4, 1919). Universal distribution of bacteria is often present; but when scanty the concentration is most obvious in the leucocytic plug filling the bronchioles, some being intra- and some extra-cellular.

The report of Sewell, Newcastle (*B. M. J.*, January 11, 1919), confirms our opinion of the origin and activities of the large mononuclear cell found in alveoli. Our sections show no evidence of hyperplasia of bronchial epithelium, but evidence of destruction is abundant. (Muir, ibid.)

II. Trachea.

Shows acute inflammatory changes with desquamation of the mucous membrane and leucocytic accumulation in the sub-mucous layer.

III. Bronchial Glands.

Show great engorgement and oedema. Vessels are shown in section distended with red blood corpuscles, and individual cells of gland tissue are separated by oedema, giving a clear appearance to the section. No abscess formation or necrosis is to be seen.

IV. Liver.

Shows varying grades of cloudy swelling, and a granular deposit of fat may be demonstrated by special staining methods and is probably due to diminished functional activity of the liver prior to death. Two cases of the series only show fatty accumulation within the liver cells, and in both of these the liver is somewhat cirrhotic. Terminal engorgment is the rule with marked dilatation of the central lobular vein and of the capillaries draining into it.

V. Kidney.

In the milder cases some degree of cloudy swelling is usually present with some terminal engorgement.

Many cases present severe microscopic damage with swelling of epithelial cells of tubules and desquamation, the tubules being filled with granular and epithelial deposit. Great engorgement of capillaries of Bowman's capsule with haemorrhage into the capsule and elsewhere throughout the kidney tissue from toxic spoiling is present. Leucocytic reaction is scanty, the damage being mainly toxic.

VI. Brain.

Apart from some capillary engorgement nothing abnormal is seen.

VII. Rectus Abdominis Muscle (Haemorrhagic).

Section shows haemorrhage spreading along the areolar tissue separating muscle bundles, with some dilatation of small vessels and capillaries. Individual muscle fibres in transverse section show some difference in taking the counter-stain (eosin), some having a violet tinge. The nuclei are definite and no swelling of muscle protein is apparent.

Leucocytic reaction is absent.

Description of Plates I–IV.

Plate I. Lung from a case of Influenza, showing large more or less circumscribed areas of haemorrhage with marked emphysema in other parts.

Plate II. Larynx and trachea from a case of Influenza, showing oedema of the glottis and acute inflammation of the trachea with an overlying membranous exudate.

Plate III. A. Section of monkey lung (Monkey 2) which had been inoculated with filtered sputum, showing haemorrhagic condition. B. Ditto, showing acute congestion with more marked reaction around two calcified areas.

Plate IV. Left lung and trachea of Monkey 2, which had been inoculated with filtered sputum, showing large haemorrhagic area in lung and marked infection of the trachea.

(The descriptions of the figures included in Plates V–XIII are printed on the plates.)

A K. MAXWELL

Plate II.

72²

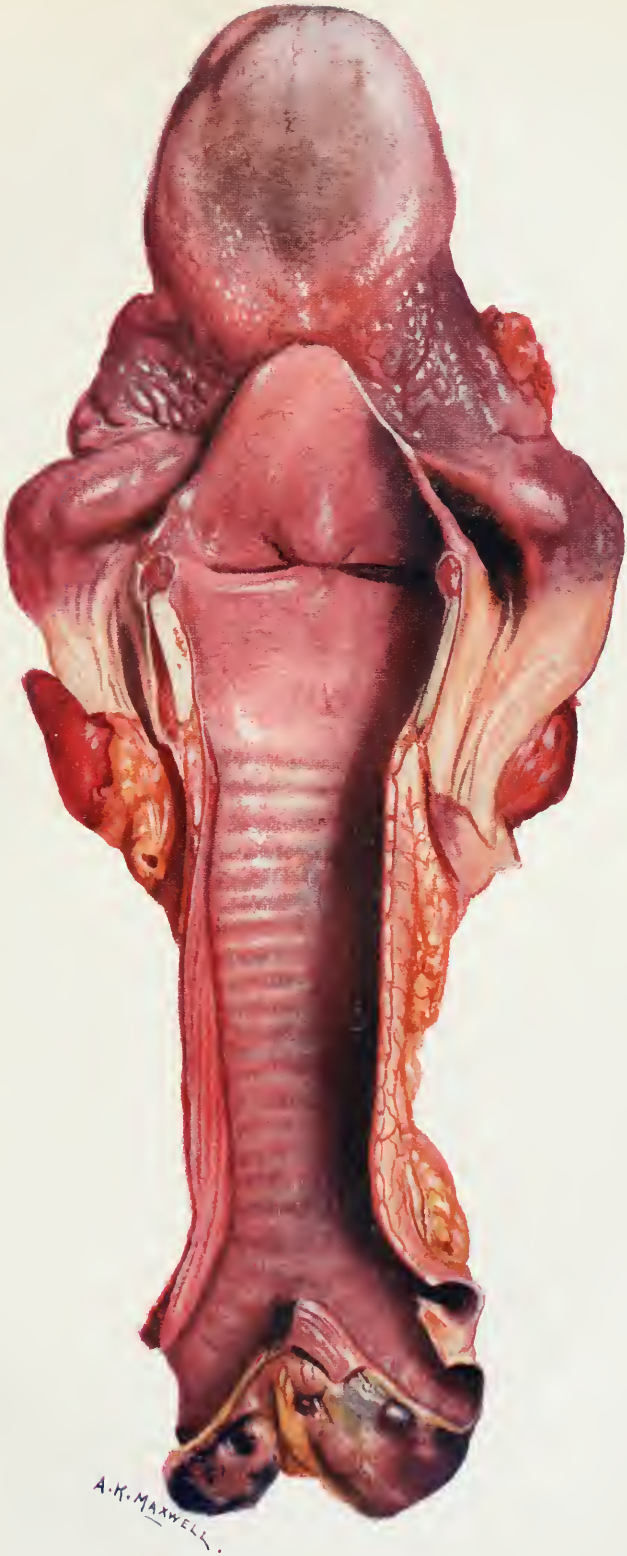


Plate III.

72

A.K.M. X 2.

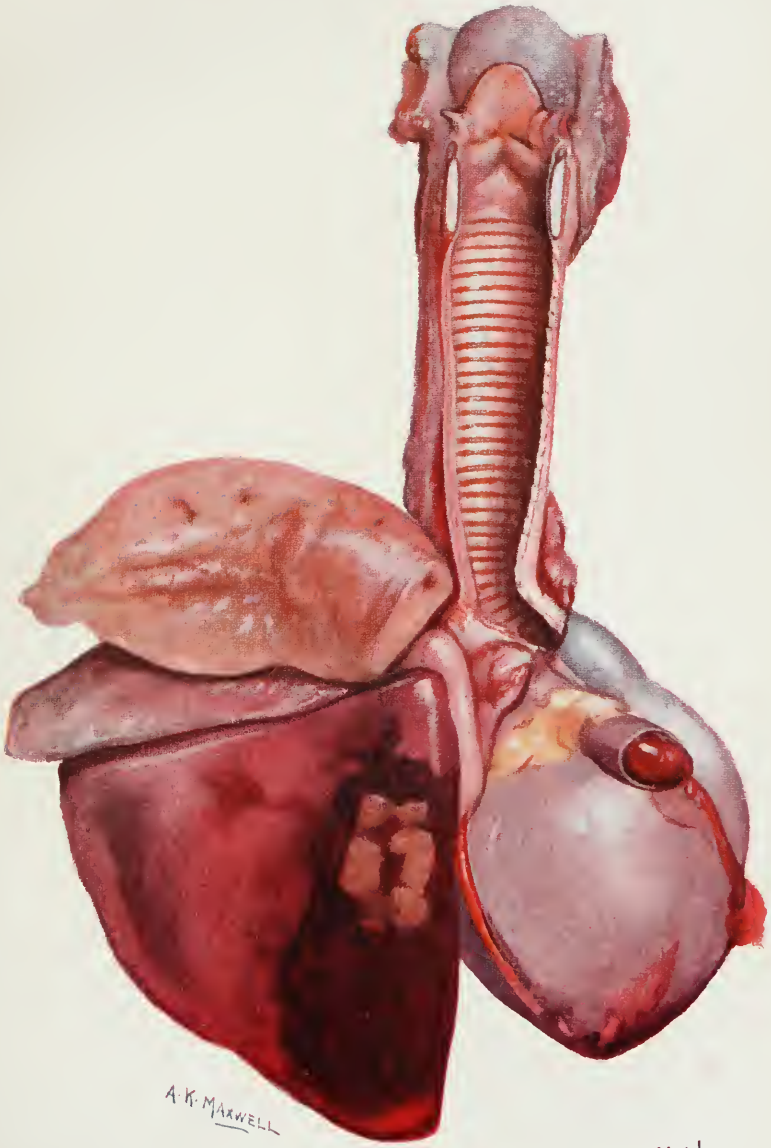
A

A.K.M. X 2.

B

Plate IV.

72 4



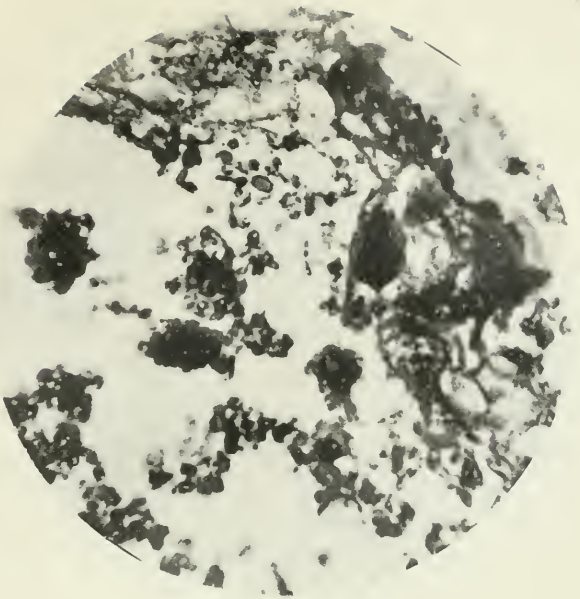
X 1½.

Plate V

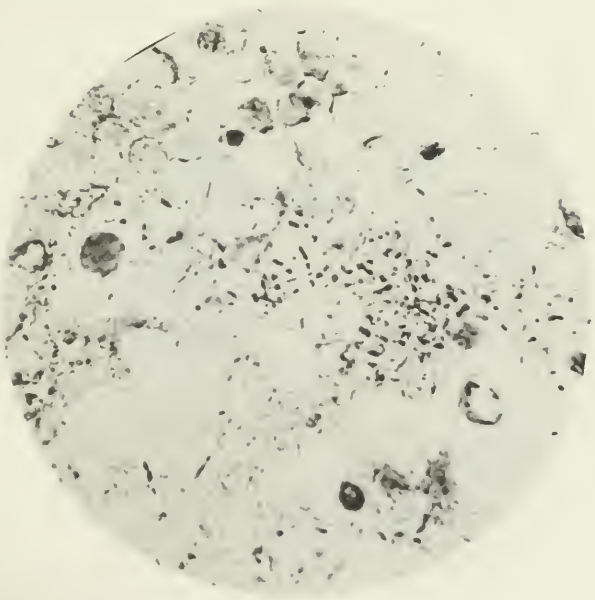
A. A Pleomorphic Diplostreptococcus isolated from a large number of cases of Influenza. From 48-hour culture (× 1500).

B. Diplostreptococcus in association with *B. influenzae*, from 24-hour culture from sputum (× 1000).

Plate VI.

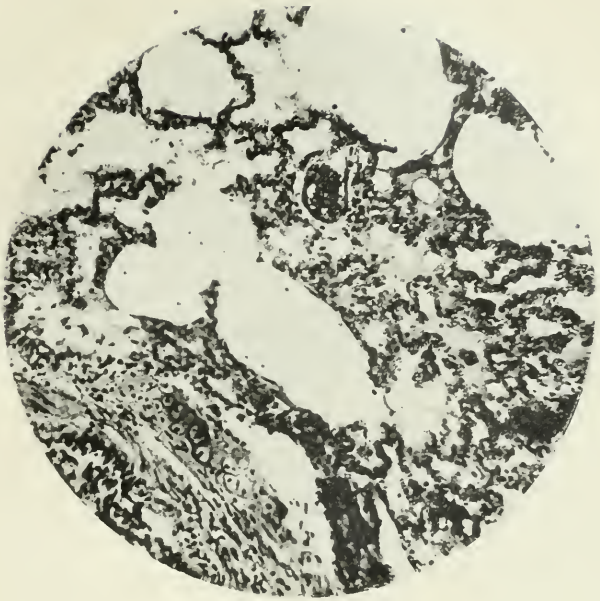


A.—Human Lung, encapsuled diplococci in section (×1500).

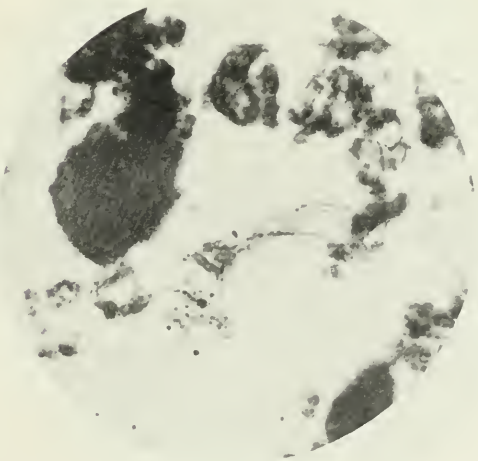


B.—Human Lung, pleomorphic diplostreptococci in inflammatory exudate (×1000).

Plate VII.

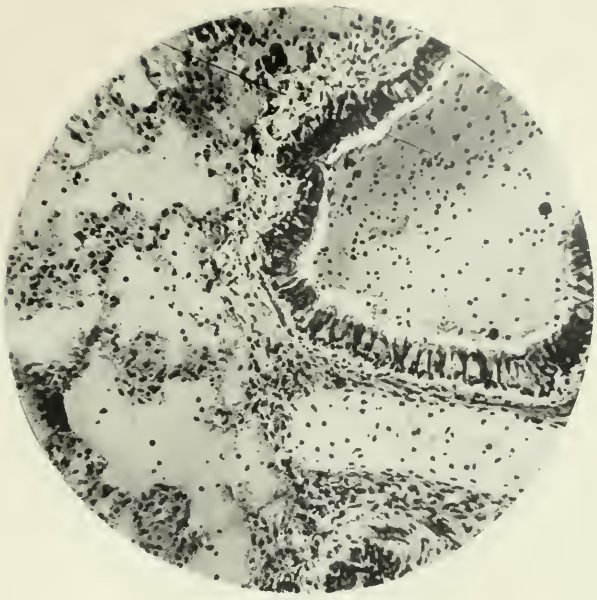


A.—Monkey Lung (Group II, No. 2) showing congestion and inflammatory exudate (×700).

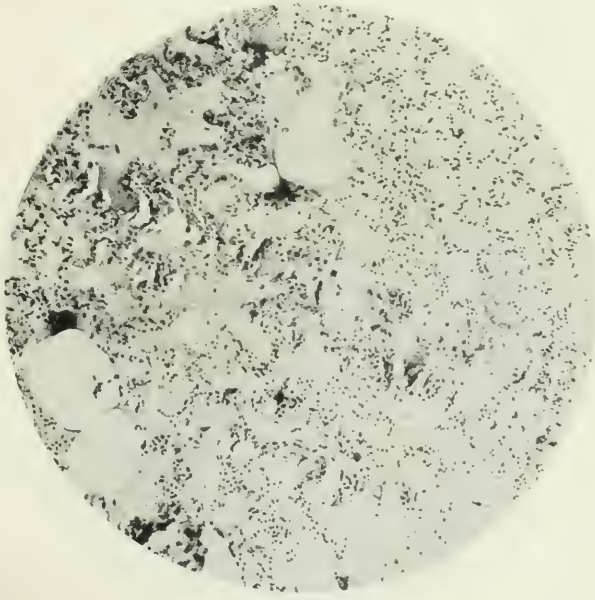


B.—Human Lung showing streptococci in section (×1000).

Plate VIII.

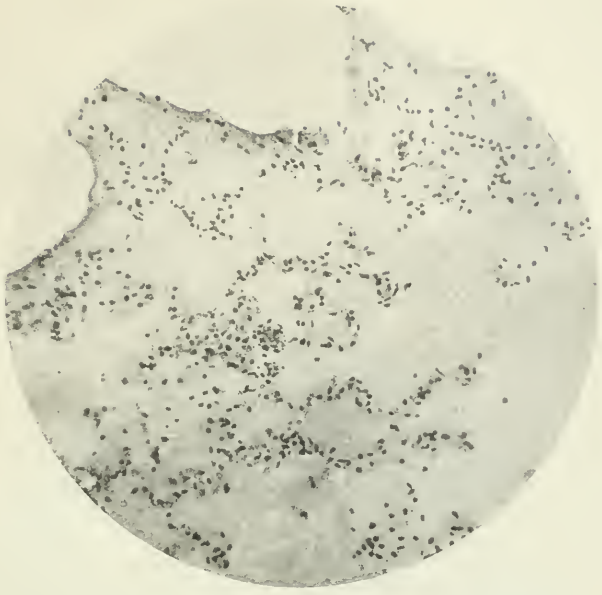


A. Monkey Lung (Group I, No. 4) showing inflammatory exudate in alveoli and bronchiole (mucous membrane intact) (×700).

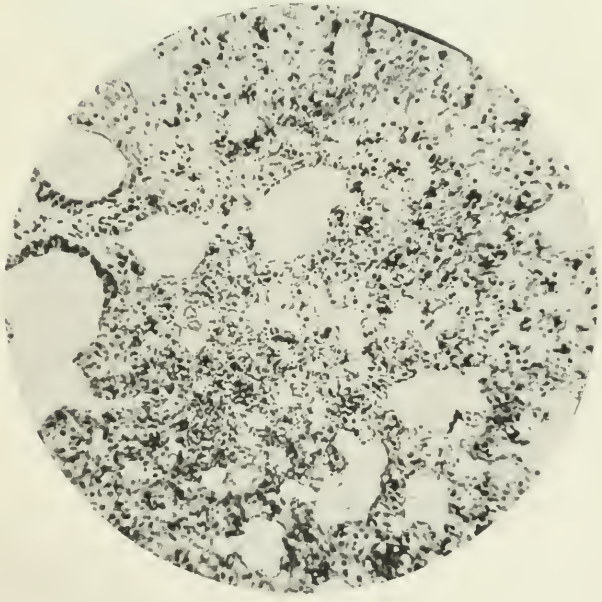


B. Monkey Lung (Group I, No. 6) showing margin of inflammatory exudate (left), clear lung (right) (×500).

Plate IX

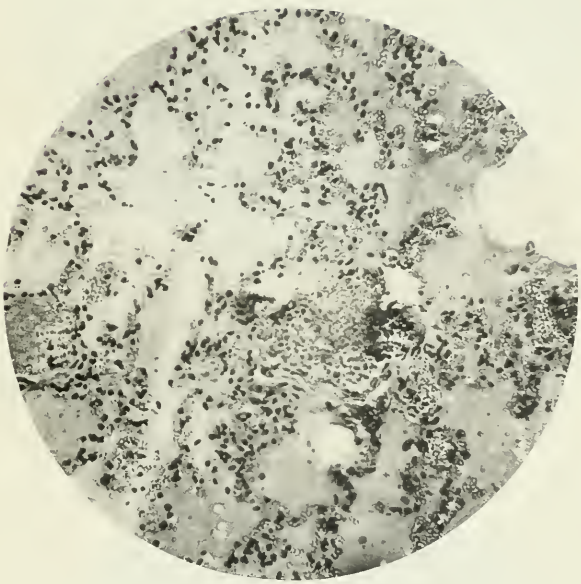


A.—Monkey Lung (Group I, No. 3) showing solution of alveolar wall and inflammatory exudate (×500).

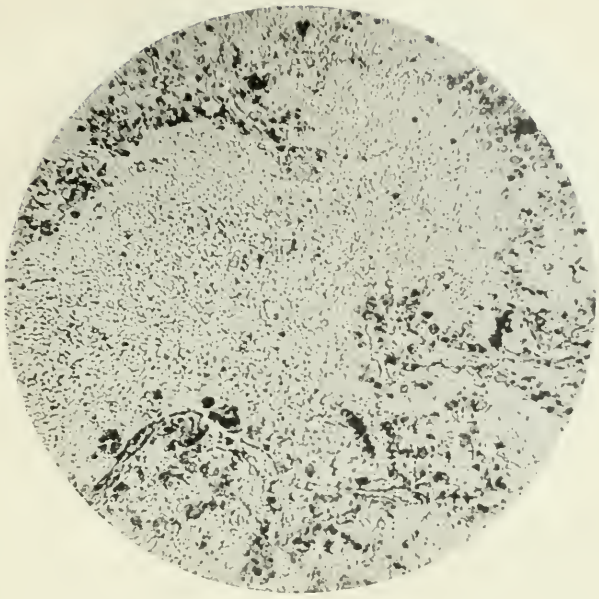


B.—Mouse Lung (W 2) showing haemorrhagic inflammatory exudate (×500).

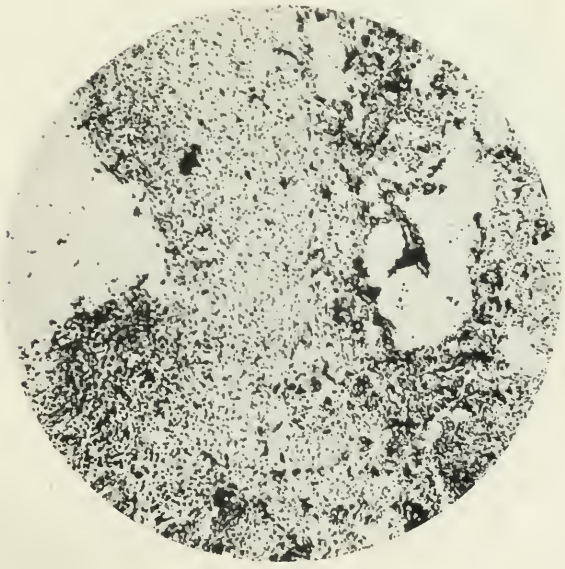
Plate X.



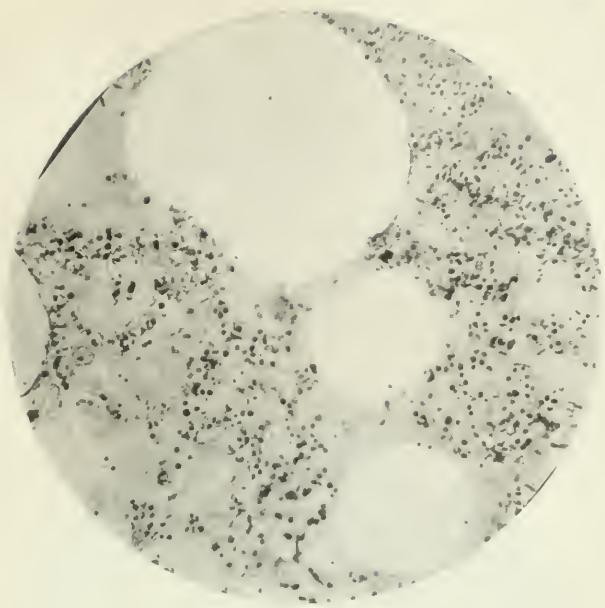
Monkey Lung (Group I, No. 5) showing intense congestion and inflammatory exudate filling alveoli of lung (×500).



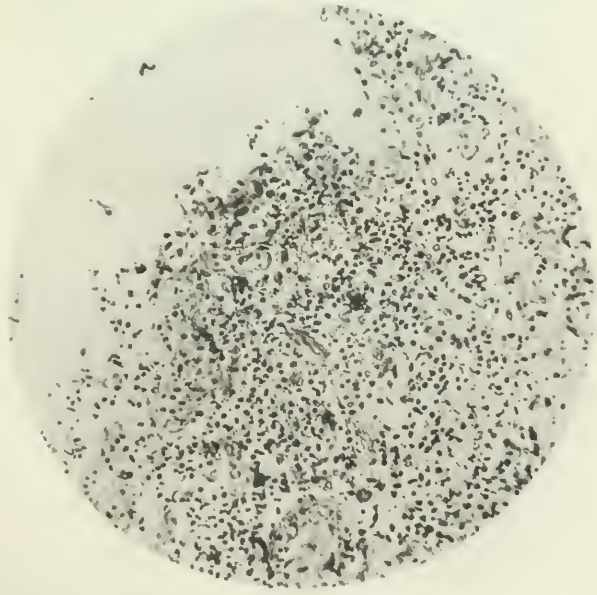
A.— Human Lung. Area of haemorrhage, showing solution and rupture of the alveolar walls and marked accumulation of red blood cells in the surrounding alveoli. Leucocytes scanty (×700).



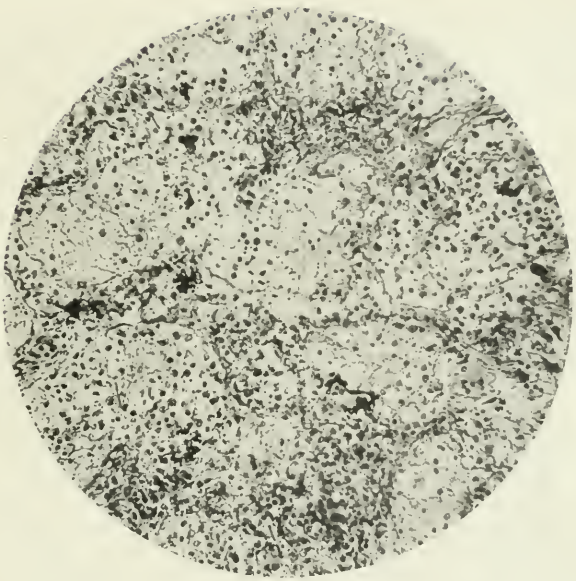
B.— Human Lung. Area of broncho-pneumonia, showing destruction of bronchial mucosa with desquamation of epithelium. Cellular reaction marked at sites of smaller bronchi (×500).



A.—Human Lung, area of oedematous pneumonia, showing alveoli filled with albuminous exudate. Leucocytic reaction not marked. (×700).



B.—Human Lung, area of multiple abscess formation, showing total destruction of bronchial mucous membrane with rupture and solution of the surrounding alveolar walls (×700).



Human Lung, area of consolidated lung of varying colour from red to grey, usually dripping at autopsy. Shows a fibrinous reticulum filling the alveoli. Leucocytic reaction present but not advanced (× 700).

PART II

4 (a). CLINICAL IMPRESSIONS OF THE PNEUMONIAS OCCURRING DURING THE INFLUENZA EPIDEMIC

BY

Major (now Colonel) C. F. Martin, C.A.M.C.

(From No. 3 Canadian General Hospital.)

The pneumonias which have occurred during the influenza epidemic of October and November 1918, have been so varied in their clinical characters that it has been impossible to group them into definite types, but the following tentative classification shows the chief types that have been noted :

(1) Cases with symptoms and more or less frank signs of pneumonia, suggesting clinically a lobar pneumonia.

In these cases the sputum may show either *B. influenzae* or organisms of the streptococcus-pneumococcus group as the predominant organism.

(2) Cases in which signs of pneumonia are indefinite and occur only in the later stages of the disease.

(*a*) Mild, or moderately severe cases, with fever lasting from four to eight days, and terminating usually by lysis. The signs of bronchitis predominate.

(*b*) Fulminating cases, fatal in from three to five days, with symptoms suggesting a general septicaemia. The respiratory tract in general shows signs of involvement only in the late stage.

(*c*) Cases with irregular intermittent fever running a severe course for one to four weeks, and terminating fatally or recovering very gradually. In these cases physical examination reveals evidence of an acute involvement of the whole respiratory tract. Signs of pneumonia appear late.

There is frequently epistaxis, pharyngitis, laryngitis, and synchronously a diffuse bronchitis of the finer tubes, and some involvement of the alveoli. Often before death there is evidence of bronchiectasis or abscess formation. The pulmonary involvement is nearly always bilateral, and the physical signs of serious pulmonary disease are usually delayed. To say the least, the ordinary methods of physical examination yield results that are far from satisfactory, and diagnosis from the most careful examination is often quite at variance with the post-mortem findings.

Clinical Features of the Disease.

Onset.

The disease frequently follows more or less exposure, but may come on with unexpected suddenness.

There is usually some malaise, with involvement of the upper respiratory tract, which may develop gradually and progressively.

Chilliness is one of the commonest early symptoms, and may last for days before serious developments occur. A genuine rigor is not so common. Herpes has not been a frequent sign in this epidemic.

Pain.

This has been much less common in the pneumonias of this series than in the ordinary lobar pneumonia with pleurisy.

As a rule, general pains over the body, and especially in the back, predominate over local thoracic symptoms, and the sensation is that of oppression rather than of actual pain.

Cough.

The cough, which is among the earliest symptoms, is at first irritating and non-productive, tracheal in type, and often so continuous as to prevent the patient from getting any rest. Apparently this is one of the frequent causes of the supervening exhaustion.

Marked hoarseness, as a part of the laryngo-tracheitis, has been frequent, and forms a striking feature of the general picture.

Sputum.

In the early stages sputum may be absent for days. It appears first as small lumps of muco-pus, somewhat viscid, and later becoming numular and more easily produced. It soon becomes of a characteristic greenish grey colour with more or less froth.

Blood is very frequently present, and there may be merely rusty sputum, or a bright red haemoptysis, sometimes copious. Not infrequently the rusty sputum is the first evidence of pneumonia. When it appears after several days, it may suggest the picture of a central pneumonia.

Cyanosis and Dyspnoea.

Practically all cases of even moderate severity show marked cyanosis, doubtless due to the widespread involvement of the finer bronchial tubes. It begins early and is progressive to the end in fatal cases, while in cases which recover it may persist for many days.

Dyspnoea is usually a later symptom. At all events it is remarkable how slow the respirations are, as recorded on the charts, even when the temperature is high for days. This of course does not apply to either the fulminating types, or to those in which the signs and symptoms suggest a lobar pneumonia. The respirations may remain only slightly increased for days, which is the more surprising in view of the involvement of the finer bronchial tubes. In not a few cases the breathing is asthmatic in type, and the auscultatory phenomena confirm this observation.

Pulse.

Considering the height to which the temperature rises, it is notable that the pulse is comparatively slow in the early stages of the disease, often being no higher than 100° for many days, and the acceleration accompanies only the later period of the disease.

Mental State.

Delirium has occurred in but a small percentage of our cases, and was then only of the low muttering type. Apathy, however, is a constant feature of the picture, and patients are often drowsy from the start and difficult to rouse.

Jaundice.

This has appeared in about 10 per cent. of the cases.

Physical Signs.

The physical signs in the chest are characteristic of the disease in so far as they are varied and unreliable. Owing to the multiplicity of the pathological changes that may occur concurrently in the same lung, the accuracy with which one may determine the underlying condition is limited.

The outstanding feature of the physical signs is this, that with an extensive infiltration of the alveoli there may be no other physical signs than those of a fine bronchitis or bronchiolitis. For four or five days, or longer, from the onset of serious symptoms, one may find nothing more than a few fine rales at both bases or in the interscapular region. Signs of bronchitis dominate the picture.

Again, for a number of days there may be no other physical signs than suppressed breathing, even when the sputum is haemorrhagic; one gains the impression then that a central pneumonia has existed, accompanied by a generalized fine or coarser bronchitis, and moderate oedema. In the fulminating cases, suppressed breathing may be the only physical evidence of involvement up to the end, though at autopsy widespread acute changes may be found.

In a number of cases where the disease was severe, and irregularly febrile for up to three weeks, there was very slight, if any, dullness, no blowing breathing, and no bronchophony, and yet there were marked dyspnoea, cyanosis, and diurnal variations of temperature between 100° and 103°. The physical signs showed evidence only of bronchitis and some oedema.

In other cases with similar irregular fever for as much as seventeen days, with dyspnoea and typical greenish sputum, the signs were those of bronchitis, with, in addition, the suppression of breath sounds in patches, but no dullness, no bronchophony, and no blowing breathing anywhere. This suppression of breath sounds may persist for many days before it is followed by even distant blowing breathing or other evidence of consolidation, while marked evidence of confluent pneumonia is always a late sign.

The suppression of breath sounds often remains for days after the temperature has returned to normal.

Percussion.

When dullness occurred it was found most frequently in the infra-scapular region, less often in the inter-scapular region or at the base. Anteriorly and at the apices dullness is quite infrequent, even late in the disease. It is rarely diffuse until shortly before a fatal termination.

Auscultation.

The most noteworthy auscultatory sign is the shortness of the inspiratory murmur, which ends abruptly and before the normal duration of the excursion. It is often more of an inspiratory grunt, while expiration is feeble and sometimes moderately prolonged. This, too, seems to be in keeping with the idea that the disease is primarily of the nature of a bronchiolitis.

As already noted, blowing breathing is nearly always a late sign. It corresponds in site to the areas of dullness, when these are evident.

The same may be said of the advent of bronchophony, which, however, is often a most valuable means of detecting areas of doubtful consolidation. Nevertheless, in many cases where autopsy revealed marked broncho-pneumonia, the vocal resonance has been unchanged.

To sum up, one may say that, save in the cases which resemble frank lobar pneumonia, the physical signs lead to the conclusion that the condition is a diffuse patchy involvement of both lungs, with considerable oedema, supervening on an invasion of the finer bronchial tubes ; later on, there is a more or less slow development of consolidation in various areas of the lung, more particularly in the upper portion of the lower lobe.

Course and Duration.

The course of the disease may be fulminating acute, sub-acute, or even almost chronic (i. e. lasting for four weeks or more), with favourable result, or otherwise. Death has occurred in four days, while in a few of our patients irregular high fever was continued for many weeks, terminating in ultimate recovery.

In the unfavourable cases the continued mild asphyxia leads to exhaustion.

Recovery usually occurs by lysis in the mild cases, by crisis in the cases simulating lobar pneumonia, and in the prolonged septic cases by all varieties of descent of temperature.

4 (*b*). PATHOLOGICAL AND BACTERIOLOGICAL FINDINGS IN FATAL CASES OF PNEUMONIA DURING THE INFLUENZA EPIDEMIC OF OCTOBER AND NOVEMBER, 1918.

BY

Major W. H. Tytler, C.A.M.C.
Captain R. M. Janes, C.A.M.C.
AND
Captain G. M. Dobbin, C.A.M.C.

(From the Laboratory, No. 3 Canadian General Hospital.)

The following report is based on observations made on a series of eighty-six fatal cases of pneumonia occurring at No. 3 Canadian General Hospital between October 1 and December 1, 1918. Bacteriological examination was carried out on material taken from the lungs at autopsy in sixty-seven of these.

I. Gross Morbid Anatomy.

The gross lesions seen at autopsy may be roughly divided into two groups, those occurring in intimate relation to the bronchial system, and the more diffuse processes.

The first groups include bronchitis, peribronchial abscess formation, bronchiectasis, and interstitial broncho-pneumonia.

Bronchitis.

Purulent bronchitis is evident in the great majority of cases, and in those of longer duration is usually very extensive. When the lung is first cut the bronchioles and smaller bronchi may often be seen to be filled with thick greenish yellow pus, which exudes copiously on pressure. In other cases it may be necessary to squeeze the lung to bring the pus into evidence, and a considerable search may be needed, but in most cases there can finally be found an area in which the bronchioles yield on pressure some beads or flakes of yellow white pus or muco-pus.

Peribronchial Abscess Formation.

In many of the lungs there may be seen scattered through the tissue, or more commonly in clusters in relation to areas of broncho-pneumonia, small white spots of 1 to 3 mm. diameter, which, on close examination, are seen to represent true abscess formation. Either they are solid and yield no pus on pressure, or they may yield a fine bead from the centre, leaving a solid yellow white margin,

or, again, the whole contents may be expressed, and with the aid of a hand lens, the wall of the cavity is seen to consist of bare lung tissue with no bronchial wall. These small white solid or semi-solid abscesses often have a striking resemblance, in the gross, to miliary tubercles. In a few cases there was extensive softening of the peribronchial abscesses, leading to the formation of numerous small cavities, giving a fine honeycomb appearance to the cut surface.

In three cases there were noted larger abscesses of 1 to 2 cm. in diameter, occurring in groups surrounded by intensely congested pneumonic tissue. These abscesses were either solid yellow, or had a yellow margin with a softened pink centre, and the general picture, particularly the intense vascular reaction about them, suggested the appearance of staphylococcus infarcts, but various stages between these and the smaller type described above were seen, and it was thought that they probably represented the same type of lesion, with a more virulent and rapidly spreading infection. In one case the microscopic examination showed the process to be apparently an infarction, possibly due to local inflammatory occlusion of vessels.

Broncho-pneumonia.

The type of nodular broncho-pneumonia seen in this series of cases seemed to be anatomically identical with that described by MacCallum and Cole in the pneumonias seen among American troops, following measles, and which they have called 'interstitial broncho-pneumonia'. This term very aptly describes the nature of the process, which, both from gross and microscopical examination, is evidently an extension of infection through the bronchial wall to the surrounding lung tissue,—not an infection of the alveoli by way of the natural air passages. In the earliest stage of the process there may be seen, scattered over the cut surface, small dark haemorrhagic areas of about 5 mm. diameter, which are raised above the surface, and rather firmer than the surrounding tissue. These may be isolated, or more commonly are seen in clusters. On pressure, fine beads of pus may often be squeezed from the centres of these areas. At the next stage these areas show, without pressure, a fine white spot at the centre of each, or larger spots with only a rim of congested tissue about them. The lung tissue surrounding clusters of these small areas shows congestion, oedema, and beginning consolidation. At a later and more commonly seen stage, the surrounding lung tissue is frankly consolidated, greyish with haemorrhagic mottling and forming irregular nodules of 1 to 5 cm. in diameter, containing groups of white spots representing peribronchial abscesses. These broncho-pneumonic patches may be scattered indiscriminately through the lung, sometimes so thickly as to recall the appearance of a tuberculous broncho-pneumonia, or, as often seen, may form definite wedge-shaped masses, with the base to the pleural surface, and showing extensive formation of fine abscess cavities. Again, several of these broncho-pneumonic nodules at the base of the lung may be embedded in a diffuse mass of oedematous secondary pneumonia, but the essentially focal character of the lesions is usually quite evident.

Bronchiectasis.

In some of the earliest cases the fine peri-bronchial abscesses were mistaken for dilated bronchioles, but this error was corrected on closer examination. In many cases of longer duration, however, and especially in areas of collapse, there seems to be a definite dilatation of the smaller bronchi, which are filled with copious greenish yellow pus. The lesion is usually difficult to diagnose with certainty.

In addition to the lesions having definite relation to the bronchial system, there are nearly always seen pneumonic lesions of diffuse type. Apart from localized areas of secondary pneumonia occurring about the firm patches of broncho-pneumonia, two main types of diffuse lesions were seen—a definitely lobular pneumonia, and a process showing intense diffuse congestion and oedema, often doubtfully pneumonic.

Lobular Pneumonia.

This condition has been very frequent during the present epidemic. The extent of the lesion varies greatly, but the appearance in detail is very constant. The area involved may comprise a single lobule, usually at the surface, a group of five to twenty or more lobules, or a massive area involving from a third to the whole of a lobe. The affected tissue is swollen, firmly consolidated, and, on section, pale grey, with a definitely granular surface, the texture and colour being precisely that of a croupous pneumonia in the grey stage. Even from the pleural surface, however, the lobular nature of the process can often be distinguished by the eye, and less often by the finger. In the latter case, the consolidated tissue is felt as a mass of firm individual nodules of a uniform diameter of about 1 cm.

On section, the borders of the individual lobules are usually very distinct to the eye, particularly at the margins of the consolidation, where pneumonic lobules partially or completely separated from the main mass may be seen. In some cases, each lobule stands up convexly from the cut surface, and in every case the feel of the cut surface is distinctly nodular. The pneumonic tissue is completely airless, but from the centres of the lobules there can often be squeezed fine beads of pus. In a few cases a combination of the bronchial lesions described with the diffuse lobular pneumonia was seen, clusters of peribronchial abscesses, with some haemorrhagic areas, being scattered through the affected lung tissue. Abscess and cavity formation on an extensive scale is common in these areas of lobular pneumonia, pointing to the presence of interstitial infection. A single lobule, or an extensive area involving many lobules, may be softened, grey pink in colour, and semi-fluid, leading to the formation of well-defined cavities, or to large, very irregular, serpiginous cavities embedded in partially softened tissue. It may be noted that these cases were usually recorded as having coughed up during life thick grey pink fluid of precisely the type seen in these cavities.

Sometimes, where the lobular process involves a whole lobe, and where the outlines of the lobules are less distinct than usual, it is

difficult to separate the condition from a true lobar pneumonia, but we believe that these lesions, as seen during the present epidemic, represent nearly always an infection occurring by the air passages, and truly lobular in nature. In most doubtful cases, other parts of the lungs show lesions more definitely bronchial in type.

Diffuse Congested and Oedematous Type.

Most cases showed in some part of the lung tissue a certain amount of congestion and oedema, either localized or diffuse, and probably often representing a pneumonic process, but there was a quite distinct type of case, in which death occurred after a comparatively short illness, showing intense diffuse congestion and oedema as almost the only lesion, with little or no evident bronchial involvement. When the condition is outspoken, the lung tissue may be almost airless, pieces sinking in water, but it can usually be almost completely collapsed on pressure, yielding copious, thick, bloody fluid with no evident pus. We believe, however, that the process represents a true pneumonia due to diffuse infection. In less advanced stages, and particularly where the process occurs as a secondary one in relation to focal lesions, it may appear only as congestion and oedema, with considerable air-holding tissue, pieces floating in water, and yielding on pressure only thin frothy blood-stained fluid. Again there may be seen, usually about areas of broncho-pneumonia, a diffuse pneumonia, on section grey, firm, very wet, and with a smooth shining cut surface.

In addition to the two groups of inflammatory conditions, lesions of mechanical origin are frequently seen, viz. collapse, which was fairly frequent in this series, and infarction, which was rare and indefinite.

Collapse.

The condition was seen in the cases of longer duration, and varied in extent from small patches at the free margins, to massive areas involving a considerable portion of a lobe. The marginal patches are usually about 2 to 3 cm. wide on the free edge, and extend for about the same distance into the lung. They are sharply outlined, dark in colour, and sometimes definitely depressed and leathery in consistence, but more often fairly firm, and suggesting the presence of a pneumonic process as well. We believe that they usually follow a pneumonic lesion, but that they are to be ascribed to the local plugging of the bronchi by thick tenacious pus. In nearly every case these areas on section show bronchioles distended with such exudate, and yielding large quantities of it on pressure. Scattered small areas of 1 to 2 cm. may be seen at the lung surface, which, on section, suggest a haemorrhagic process, but which microscopically show definite collapse.

More massive collapse is seen where pleural effusion is extensive, and in six cases we noted the occurrence of a type of collapse identical with that described by Colonel T. R. Elliot in chest wound cases. The area of collapse is seen externally as an irregular strip 2 to 10 cm. wide running from the upper posterior part of the lower lobe diagonally downwards and forwards, through the lower free margin and

on to the diaphragmatic surface. This area corresponds to the distribution of one of the branches arising from the main bronchus to the lower lobe, the second branch from the top. In three cases this condition was bilateral, and the remainder of both lobes showed extensive pneumonic lesions. In two cases it was unilateral, of which one was a case of chest wound, in which pneumonia with this collapse had developed on the opposite side. The tissue involved was in no case completely collapsed, but was dark red in colour, leathery, and relatively airless, with the smaller bronchi dilated and filled with thick tenacious muco-pus. The explanation of the distribution of this collapse is obscure, for in no case was there any plugging of the main bronchial branch or of its larger branches.

Infarction.

Where areas of solid lobular or broncho-pneumonia involve a free margin, this border may occasionally show a condition suggesting haemorrhagic infarction, which we ascribe to local occlusion of the vessels as part of the interstitial inflammatory process. We have noted above the occurrence of groups of abscesses, some of which suggested in the gross the appearance of septic infarcts, and one of which microscopically seemed to be of that nature.

Haemorrhagic Pneumonia.

Apart from superficial more or less well-defined areas which suggest infarcts, a number of cases showed more widely scattered and much more indefinite haemorrhagic areas, the nature of which was more doubtful. These usually were of 1 to 3 cm. diameter, with indefinite borders, and often soft and incompletely consolidated. Many of these probably represented an early stage of the interstitial broncho-pneumonia described, although no evidence of purulent bronchitis could be seen. Again, in the pneumonias of the diffuse, wet, congested type, there might be found very indefinite masses which were more solid and more haemorrhagic than the surrounding tissue. In two cases numerous well-defined, strikingly globular masses of 2 to 5 cm. diameter were seen. These on section showed uniformly circular outlines, and were composed of firm, fairly dry, dark reddish black solid tissue, bordered by pale pneumonic tissue. At the centre of each mass was a blood-vessel of 3 to 5 mm. diameter, and a small bronchus placed more eccentrically. In no case was there any thrombosis of the central vessel. Microscopic sections from the centre of one of these areas showed both vessel and bronchus free from exudate, but surrounded by a central area of interstitial pneumonia. The origin of the process could not be definitely determined.

Emphysema.

There was usually some evidence of emphysema at some part of the lungs, but it was seldom extreme, and was usually more or less masked by oedema and congestion.

Emphysematous bullae were not infrequent at the anterior free margins. One case showed bilateral local emphysema in the lower lobes, with the same distribution as the peculiar type of collapse

noted above, i.e. a strip running downwards and forwards from the apex of the lobe to the diaphragmatic surface, the lung tissue in front and behind being pneumonic.

Gross Anatomical Distribution of Lesions.

A most constant finding was the localization of the more advanced lesions in two positions :

1. At the lower margin of the upper lobe, often as a strip extending from the apex along the lower border to the anterior margin.
2. At the vertebral border of the lower lobe.

Apart from these two positions, the lesions were commonly more advanced and extensive in the posterior parts of the lungs.

The peculiar distribution of collapse and of emphysema in certain cases has already been noted.

Pleural Cavities.

Non-purulent effusion was seen in 40 per cent. of cases, and varied from 50 c.c. to a litre. In seven cases, or 8 per cent., the quantity was 500 c.c. or more. The fluid was thin, clear, and usually brownish or definitely haemoglobin stained. In 20 per cent. of cases thin, slightly purulent effusion was seen, and in three cases, or 3·5 per cent., definite empyema with thick pus.

Fibrinous or fibrino-purulent exudate occurred on the pleural surfaces in 60 per cent. of cases.

Sub-pleural haemorrhages occurred in 68 per cent. (the figure is probably higher than this, for in some cases their presence or absence was not recorded). These were usually petechial, but in a considerable number of cases there were also seen larger patches up to 3 cm. showing a delicate, thin, lace-like or flower-like haemorrhagic layer under the pleura. More dense haemorrhagic plaques were seen over areas of broncho-pneumonia. Haemorrhagic lesions were often seen on the parietal as well as on the visceral pleural surfaces.

Larynx and Trachea.

In the majority of cases the larynx was pale and neutral, but shortly below it the trachea showed diffuse congestion, becoming progressively more intense as it was followed down to the bifurcation and on into the main bronchi. Fine sub-mucosal haemorrhages were not infrequently seen. In a certain proportion, about 20 per cent. of the cases in which it was examined, the larynx also showed diffuse congestion, and these were usually cases in which laryngitis had been particularly evident during life.

II. Microscopical Examination.

The histological examination of the material obtained is as yet very incomplete, but the sections that have been studied confirm, broadly, the impressions given of the nature of the processes from gross examination. The bronchial lesions are rather more extensive than appeared in the gross, and in some cases in which it was thought that the bronchial walls were intact, the sections show at least beginning destruction of the walls. In more advanced lesions the

bronchiole and its surrounding tissue is converted into an abscess bordered only by pneumonic alveoli. The early stages of the broncho-pneumonic process show bronchioles filled with pus and more or less devoid of walls, surrounded by peribronchial connective tissue in which are numerous large dilated blood-vessels, and only occasionally a definitely haemorrhagic process. Diffuse cellular infiltration, both leucocytic and lymphocytic, is seen, and the surrounding alveoli are filled with fibrinous and purulent exudate. The later stage of the broncho-pneumonia shows a complex and inconstant picture, but the cellular exudate in the alveoli usually shows a considerable proportion of large mononuclear cells, many of which can be definitely seen to have arisen from the alveolar epithelium, which is swollen and desquamated, often as a uniform layer. In this way giant cell-like masses may be formed.

The lobular pneumonia shows microscopically less fibrin than might have been expected from the gross. Diffuse purulent exudate is seen, often with a considerable proportion of mononuclear cells, probably epithelial.

The diffuse congested wet type shows extensive oedema and haemorrhagic exudate, and usually scattered leucocytes in varying numbers, and also areas of greater leucocytic concentration.

The collapsed areas may show fairly extensive beginning overgrowth of connective tissue and blood-vessels, and giant cell-like masses may be seen.

III. Bacteriological Examination.

In making cultures from the lungs at autopsy the material which was selected by preference was the pus or muco-pus which was squeezed from the fine bronchi in the pneumonic areas. The lung was cut through, and then, while one person squeezed a favourable portion, another picked up the beads or flakes of pus with a capillary pipette as they were expressed from the bronchi. The co-operation of two workers in this way saved unnecessary contamination of the material. Where there was no purulent bronchitis evident, and in most cases where there was definite consolidation, cultures were also made from the involved areas by puncturing the external surface of the lung after searing.

The material so obtained was spread on plates made by adding about 10 per cent. of citrated blood (citrate sol. and blood—equal quantities) to trypsin agar, the plates being well dried before use. For the isolation of *B. influenzae* we much prefer to use unaltered blood. The colonies of the bacillus are undoubtedly much finer than with the various forms of altered blood (trypsinized blood, heated blood, &c.), but this character makes them more easy to distinguish from streptococci, and, in particular, colonies of pneumococci or streptococci are easily distinguished by the changes which they produce in the colour of the blood. In fact, almost the only other colonies which closely resemble those of *B. influenzae* are those of 'indifferent' streptococci, i. e. those producing no change of blood, and these were rare in the series reported. The colonies picked from the original plates were planted either on fresh blood agar, or on

trypsinized or heated blood agar, usually on a fresh blood agar plate for the first transplant as streptococci or pneumococci, the commonest source of contamination in picking the fine colonies, are ruled out without the necessity of smearing the resultant growth. Except where *B. influenzae* was greatly predominant and well isolated several colonies were usually picked. Thirty or forty such colonies may be planted on one blood agar plate by squaring off the bottom of the plate with a grease pencil.

The most striking feature of the bacteriological results in the series has been the almost constant presence of Pfeiffer's bacillus. Thus, from the lungs of sixty-seven cases examined, the organism was isolated in fifty-six, in three cases typical colonies were seen on the plates and their nature confirmed by smears, although the organism was not isolated in pure culture, and in one further case, in which the lung plate was too thickly overgrown to allow of isolation of *B. influenzae*, the organism was recovered from the heart blood. Thus the organism was certainly present in sixty cases, or 90 per cent. Allowing for errors of technique unavoidable in a series of this size, such as the occasional plate which is too thickly sown, this means that the bacillus was practically constantly present. In 45 per cent. of the cases *B. influenzae* was recorded as the predominant organism on the plates, and in many cases it was almost pure.

The diagnosis of pneumococcus was made on the presence of capsules and the fermentation of inulin. Owing to shortage of this material it was impossible to test all the possible organisms isolated, and all organisms of the pneumococcus-streptococcus group which produced a green colour on blood and which were not tested on inulin, are included in the figures given in the charts as ' Pneumococcus or Green Streptococcus '. Organisms showing no capsule and not fermenting inulin, and producing a green colour on blood, are classed as ' Green Streptococci '.

Among the figures for pneumococcus are included three cases which yielded typical *Streptococcus mucosus*. These cases were all recognized in the gross as being probably due to this organism, since we had seen two similar cases in June of this year. They showed solid massive lobular pneumonia, the cut surface of which yielded very copious thick, pinkish grey, very mucoid fluid.

A striking feature of the results has been the great rarity of haemolytic streptococci. These were isolated in only five cases, and in only three were they predominant or in sufficient numbers to justify their consideration as a prominent cause of the lesions. This is the more striking in view of the fact that several other workers have described pneumonias of apparently the same type anatomically as those seen in this series, in which the haemolytic streptococcus was almost constant, and in which the lesions noted were considered as characteristic of infection with this organism. Thus Cole and MacCallum (1), in describing the broncho-pneumonia following measles in American troops, give a picture of the areas of ' interstitial broncho-pneumonia ' which is identical with that shown by the same type of lesions in our series. They found, however, haemolytic streptococci in every case, and appear to consider this well-defined lesion as characteristic for the organism. Again, Fildes, Baker, and

Thompson (2), after describing an autopsy which they give as a type of the pneumonia in the present epidemic, say ' The organism which is immediately responsible for the above pathological picture is a haemolytic streptococcus '. The case described corresponds to those which we classed as ' diffuse, wet, congested pneumonia ', and showed also haemorrhagic masses of a type which we have noted. Among twenty-one cases of this class in our series a haemolytic streptococcus was recovered, it is true, more often than in the other types of pneumonias (see Table V), but even in these it occurred in only 14 per cent. of cases, while in thirty-seven cases showing the interstitial broncho-pneumonia of Cole and MacCallum, it was present in only 2·7 per cent.

Keegan (3) reported twenty-three fatal cases from an American Naval Hospital in Massachusetts, from 82 per cent. of whom *B. influenzae* was recovered at autopsy, while the remainder showed haemolytic streptococci. Pneumococcus, however, was the most common secondary invader (56 per cent.).

Next to *B. influenzae*, staphylococcus was the most frequently found organism. In 21 per cent. of cases it occurred in predominant numbers, usually on plates from bronchial pus.

An analysis of the relation of the type of organism isolated to the type of lesion present (Table V) does not reveal any features striking enough to definitely ascribe any type of lesion to infection with any one particular organism. The only difference worthy of consideration is the higher proportion of haemolytic streptococcus in the wet congested type. It must be remembered, however, that the total number of such streptococci isolated was very small.

Comparison of results obtained with material from various types of lesion in the same lung have also failed to give much light on this question. There was usually no marked difference between the plates made from bronchial pus and those from diffusely consolidated tissue, with the exception that staphylococci were sometimes more numerous in the bronchi. Our results have not enabled us to answer the question as to whether *B. influenzae* by itself can cause diffuse pneumonia, but in several plates from such lesions we have found it in predominant numbers, and in one case, puncture of a solid grey massive lobular pneumonia, with little bronchitis, gave a confluent growth of *B. influenzae*, pure save for six or eight colonies of pneumococcus. In this connexion it must be remembered, of course, that in the late stages of ordinary lobar pneumonia it may be difficult to isolate the pneumococcus from the affected lung.

Keegan, in twenty-three cases of pneumonia, got *B. influenzae* in pure culture six times by lung puncture at autopsy, and thinks that it was the cause of the pneumonia.

To sum up, then, we think that the constant presence of *B. influenzae* in the condition entitles it to be considered as the causative agent, even if only in the sense that it prepares the way for other invaders. We think that it is always responsible for the bronchitis, and it is probable that it may also cause pneumonic lesions by itself. The nature of the secondary infection has been too varied to admit of characterizing any one organism as a specific agent, but we think that the pneumococcus played the most important part in the

pneumonias of our series. It is not justifiable to ascribe any of the lesions noted, with the exception of the bronchitis, to one particular organism. The occurrence, with similar lesions, of different organisms in different parts of the world, would seem to indicate that the nature of the secondary infection depends largely on the relative prevalence of the various members of the pneumococcus-streptococcus group in the region in question.

REFERENCES.

(1) Cole and MacCallum, *J. Am. M. Ass.*, 1918, **70**, 1146–56.
(2) Fildes, Baker, and Thompson, *Lancet*, Lond., Nov. 23, 1918.
(3) Keegan, *J. Am. M. Ass.*, 1918, **71**, 1051.

Table I.

Relative Frequency of the Gross Anatomical Lesions in Eighty-six Autopsies.

	No.	%
Purulent bronchitis present	67	78
Purulent bronchitis pronounced	21	24
Peribronchial abscesses	38	44
Interstitial broncho-pneumonia	51	59
Lobular pneumonia present	51	58
,, ,, massive	35	43
,, ,, isolated	27	31
Diffuse wet congested pneumonia	25	29
(Of these, purulent bronchitis present in 14, or 56%)		
(Absent or doubtful in 11, or 44%)		
Collapse present	22	26
,, local	12	14
,, massive	5	6
Following distribution of 2nd tertiary bronchus to lower lobe	6	7
Haemorrhagic pneumonia (including doubtful broncho-pneumonic areas)	13	15

	No.	%
Pleural effusion, non-purulent	35	41
Pleural effusion, thin, slightly purulent	17	20
Definite empyema	3	3·5
Fibrinous and fibrino-purulent pleurisy	51	59
Sub-pleural haemorrhages	53	62

	Larynx.	*Trachea.*	*Bronchi.*
Nos. recorded	15	20	34
Congested	4(27%)	20(100%)	32(83%)

Table II.

Bacteriological Results. Direct Smears of Material from Lungs of Fifty-two Cases.

	Present.		*Predominant.*	
	No.	%	*No.*	%
Definite Gram-negative bacilli with characteristic morphology of *B. influenzae*	35	67	19	36
Organisms of streptococcus-pneumococcus group. Capsules stained	18	35	10	19
Capsules doubtful, or not examined for capsules	7	13	2	4
Capsules absent	21	40	12	23

Gram-negative cocci were seen in only a small number of cases (less than 10%). A few cases showed probable staphylococci, but it was seldom possible to be certain of these organisms.

Table III.

Cultures from Lungs in Sixty-seven Cases.

	Present.			*Predominant on Direct Plate.*	
	No.	%		*No.*	%
B. influenzae, isolated	56	84	88 %	30	45
B. influenzae, not isolated, but colonies seen on plate and smears from these typical (1)	3	4			
Staphylococcus (nearly always *aureus*)	51	72		14	21
Pneumococcus, isolated	17	25		5	7·5
Green streptococcus, isolated (2)	17	25		3	4·5
Pneumococcus or green streptococcus, undetermined (3)	23	34		5	7·5
Haemolytic streptococcus	5	7·5		3	4·5

'Indifferent streptococci', i. e. those producing no change on blood-agar, were isolated in four or five cases, never as the predominant organism.

Gram-negative cocci were seen in small numbers on a considerable number of plates, but were never predominant, or even in relatively large numbers.

Notes.

(1) In one case, in which *B. influenzae* was not found in the lung, it was recovered from the heart blood, making the total cases from which the organism was recovered at autopsy 60 or 90 %.

(2) Under 'green streptococcus' are classed the organisms which produce a green colour on blood-agar, have no capsules, and do not ferment inulin.

(3) Owing to our supply of inulin having become exhausted, a number of organisms of this group could not be tested.

Table IV.

Cultures from Heart Blood in Fifty Cases.

Positive, 25 or 50 %	*No.*	%
B. influenzae, isolated	2	4
Pneumococcus	4	8
Green streptococcus	1	2
Pneumococcus or green streptococcus, undetermined	6	12
Haemolytic streptococcus	2	4
Staphylococcus aureus	8	16

In the remaining two positive cultures organisms suggesting *B. influenzae* were seen, but were not isolated.

Table V.

Relation of Organisms isolated to Type of Lesion present.

	Purulent Bronchitis.	*Peri-bronchial Abscesses.*	*Interstitial Broncho-pneumonia.*	*Lobular Pneu-monia.*	*Wet Congested Type.*	*Total Cases.*
Numbers examined.	52	30	37	39	21	67
B. influenzae	92 %	97 %	95 %	85 %	76 %	88 %
Staphylococcus	81 %	77 %	84 %	77 %	76 %	72 %
Pneumococcus	30 %	20 %	22 %	31 %	27 %	25 %
Green streptococcus	25 %	33 %	32 %	23 %	19 %	25 %
Pneumococcus or green streptococcus, undetermined	33 %	37 %	32 %	31 %	29 %	34 %
Haemolytic streptococcus	6 %	6·6 %	2·7 %	10 %	14 %	7·5 %

5. REPORT ON THE BACTERIOLOGY AND PATHOLOGY OF 46 FATAL CASES OF INFLUENZA

BY

Major J. W. Patterson, R.A.M.C., No. 5 General Hospital.
Dr. E. Marjory Little, att. R.A.M.C. } No. 25 Stationary
Miss S. E. Williams, A.A.N.S. } Hospital.

WITH A NOTE ON THE PREPARATION OF MEDIA FOR THE CULTIVATION AND STUDY OF *B. INFLUENZAE* (PFEIFFER)

BY

Dr. E. Marjory Little, att. R.A.M.C.
AND
Miss S. E. Williams, A.A.N.S.

During the past month 63 fatal cases of 'influenzal' bronchopneumonia occurred in No. 5 General Hospital.

When our bacteriological methods of investigation became stabilized, a series of 46 consecutive cases was submitted to analysis. The results are summarized in the succeeding tables.

I. Methods.

Smears were made from the bronchi and from portions of lung which exhibited haemorrhagic engorgement, consolidation, pus, or any other abnormal feature. The smears were stained by Gram's method, and the findings noted. Cultures were made on rabbit's blood-agar plates, subsequent subcultures being made on slopes of the same medium. A series of preliminary experiments showed that rabbit's blood was superior to human blood for growing Pfeiffer's bacillus. In studying the organisms present in lung or bronchi, a series of strokes was made on the blood-agar plates, and after incubation for 18 to 24 hours the colonies were examined and subcultures made. Blood cultures from the heart were also made in 44 cases.

In the earlier cases an attempt was made to study the organisms occurring in parts of lung tissue exhibiting different stages of bronchopneumonia. The results indicated that this was not a fruitful line of investigation, and was discontinued.

II. Summary of Results of Bacteriological Examination.

1. *Blood Cultures.*

No. of Examinations made.	*Organism recovered.*				
	B. Influenzae.	*Pneumococcus.*	*Streptococcus.*	*Staphylococcus.*	*No Growth.*
44	1 case	12 cases	1 case	1 case	29 cases

2. *Bronchi and Lungs.* Table showing the organisms seen in direct smears from the organs, or subsequently isolated on cultivation.

No. of Examinations made.	*Organisms recovered.*			
	B. Influenzae alone.	*B. Influenzae + Pneumococci.*	*B. Influenzae + Streptococci.*	*B. Influenzae + Pneumococci. + Streptococci.*
46	8 cases	19 cases	3 cases	15 cases

With one exception, *B. influenzae* was recovered from every case, either alone or associated with the pneumococcus, or streptococcus, or both.

In addition a Gram-negative coccus was seen or isolated in 29 cases; it was always associated with one or more of the organisms mentioned above.

3. Table showing the relative frequency with which the various organisms were seen in direct smears, or cultivated from (*a*) the lungs, (*b*) the bronchi.

	B. Influenzae.	*Pneumococci.*	*Streptococci.*	*Gram-negative cocci.*
Lungs	36	26	14	14
Bronchi	42	28	17	24

4. Summary showing the bacteriological results of the microscopical examination of direct smears, and of cultivation on blood-agar, of the lung and bronchi of 46 cases.

No. of Cases.	*Lung.*								*Bronchus.*							
	Direct Smear.				*Culture.*				*Direct Smear.*				*Culture.*			
	B. Influenzae.	*Pneumococcus.*	*Streptococcus.*	*Gram-negative cocci.*	*B. Influenzae.*	*Pneumococcus.*	*Streptococcus.*	*Gram-negative cocci.*	*B. Influenzae.*	*Pneumococcus.*	*Streptococcus.*	*Gram-negative cocci.*	*B. Influenzae.*	*Pneumococcus.*	*Streptococcus.*	*Gram-negative cocci.*
46	14	14	2	10	36	23	14	7	25	21	3	25	40	14	17	13

5. The following chart shows the relationship of the bacteriological findings in the bronchi and lungs with reference to the duration of illness.

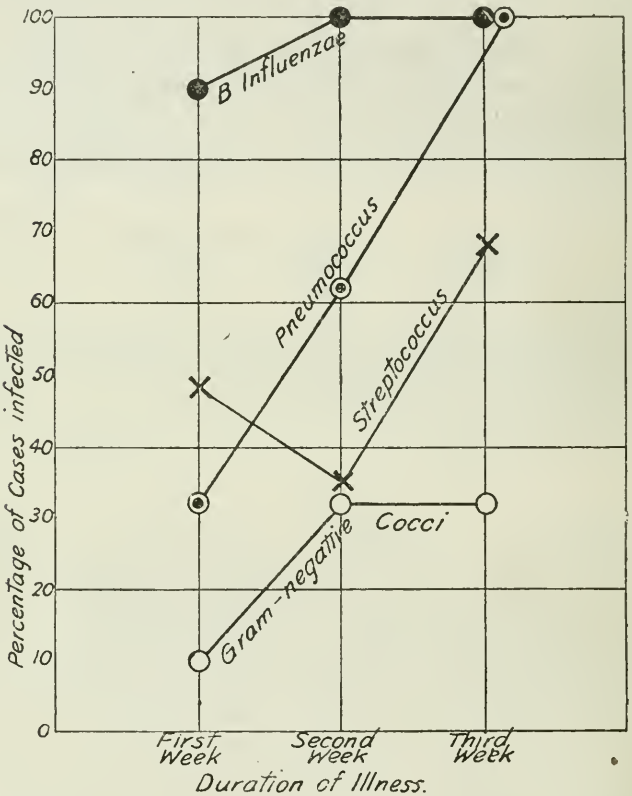
It will be seen that, while *B. influenzae* is practically constant, infection with pneumo- and streptococci increases in cases of longer duration; the Gram-negative cocci are apparently of small importance.

III. General Post-mortem Appearances.

Often frothy sanious fluid was exuding from the mouth and nostrils. The veins of the neck were engorged and full of dark fluid blood. On opening the thoracic cavity, the front of the turgid

lungs pushed up, usually full of air and crackling ; and often rupture of air vesicles had taken place, giving patches of acute emphysema, pallid beneath the pleura. There were frequently small areas of subpleural haemorrhages.

In 4 cases there was a considerable amount of dark straw-coloured fluid free in one pleura. In these cases, the pleura affected had patches of soft greenish-yellow thick fibrin scattered over the lower parts of the lung and between the lobes. Twenty-four other



cases showed recent soft fibrinous adhesions scattered over one or both lungs ; in some instances these were very dense, although recent, and in tearing through them quantities of blood-stained fluid exuded from the mouth and nostrils, as it was expressed from the lung and bronchioles. Three other cases had old firm fibrous adhesions of a previous pleurisy.

Total recent pleural involvement, 28 cases (60 per cent.). In the remaining cases the pleurae in front were pale, showing sometimes emphysema and petechial haemorrhages as described above ; and posteriorly, over the engorged or consolidated lung, the pleural surface had lost its glistening appearance, and was of a dark plum colour.

Lungs.

The most striking feature was the general engorgement and waterlogged condition of the lungs ; except in the grey consolidated patches, there was a profuse exudation of frothy sanious fluid from the cut surface. In extricating the lungs, especially when pleural adhesions were present, frothy blood-stained fluid was expressed from the bronchi and poured from the mouth.

1. To this primary *inflammatory oedema and congestion* were added the following types of broncho-pneumonic involvement.

2. *Peribronchial type.* In the early stages this condition showed as small bright-red spots of consolidation about 5 mm. in diameter surrounding a small bronchus. On palpating the lung through the pleura or passing the finger over the cut surface, the impression was given of small knots in the lung of firm consistency, resembling the feel of miliary tubercles. This condition frequently remained limited in extent, becoming grey and later softening, so that in the late stages the lung surface was pitted with small discrete abscesses.

3. *Broncho-pneumonic type.* Here the cut surface of the lung amidst general engorgement and oedema showed firmer raised bright-red areas varying in diameter up to 25–40 cm. Later these areas became larger, dark-red, and confluent. In the next stage greyish-red patches were evident, and in some instances the confluent greyish-red massive areas resembled lobar pneumonia, but the lobe showed places in various stages from dark-red areas to parts where softening and abscess formation was taking place. In some instances the whole alveolar part of the lung was diffluent, and abscesses up to 50 cm. in diameter were present, full of broken-down lung tissue and traversed by strings of more resistant bronchi.

4. *Purulent bronchitis.* From parts of the lung in all stages of involvement worms of yellowish pus could often be expressed from the small bronchi.

5. *Acute emphysema.* Along the free borders of the lungs the air vesicles were frequently ruptured and confluent.

In one case, whose bronchitic signs dated from only two days before death, only one small area of bright-red consolidation near the hilus of the left lower lobe was found in addition to a tremendous haemorrhagic engorgement of the whole of the lungs. In all other cases protean combinations of the pathological varieties cited above were found throughout the lungs. On the whole, however, the parts dependent in the dorsal decubitus showed the most widespread and farthest developed involvement.

In one case only a small infarct was discovered ; it was situated on the anterior border of the left upper lobe. Two cases showed definite evidence of tubercle, one an old calcified nodule in the apex of the right upper lobe, the other an acute miliary tubercle scattered widely throughout the lungs. In the latter, tubercle bacilli occurred in the smears, and cultures showed the presence of *Bacillus influenzae*.

Respiratory Tract.

In all cases the large bronchi contained frothy bloodstained fluid, and showed congestion of the mucous membrane. In many cases

this congestion was intense, and extended up to and involved the epiglottis, being accompanied at times by submucous haemorrhages. In cases of longer standing, erosion and ulceration of the vocal cords had occurred.

Heart.

The cavities of the right side were always much dilated and flabby, distended with dark blood, or often with firm white clot extending to the root of the pulmonary artery. The left ventricle was usually firm and contracted; but in 13 cases (30 per cent.) the muscle of the left ventricle was also softened and flabby. No acute involvement of the valves was observed. In only one case were sub-pericardial haemorrhages noted; and no instance of excess of fluid in the pericardium or of pericarditis occurred.

Liver.

The liver was always considerably engorged. A constant observation was the presence of patches of degeneration in the liver. In cases examined even within two or three hours of death, small subcapsular areas of yellowish degeneration occurred, principally on the upper surface of both lobes and at the free anterior border, extending sometimes to a depth of 2–3 cm. In some instances the degeneration was widespread throughout the liver, but this may have been due to early post-mortem changes. In two cases recent fibrinous adhesions of the diaphragm to the upper surface of the right lobe had occurred.

Spleen.

The spleen was small and firm in 22 cases, softened in 14 cases, and large and softened in 10 cases.

Adrenals.

The adrenals in 20 cases were observed to be friable; in one case both adrenals showed haemorrhagic involvement of the whole gland.

Kidneys.

The kidneys, beyond general engorgement, and some oedema of the cortex, showed acute involvement in only one case, in which there was a recent exacerbation of a chronic nephritis.

Stomach and Intestines.

In one case with a clinical history of haematemesis, the gastric veins were distended and there were numerous submucous haemorrhages on the stomach wall. In the remainder, these organs appeared normal.

Brain.

In one early case with symptoms of meningism, the brain and medulla presented no macroscopic abnormality, and the cerebrospinal fluid on culture remained sterile.

The post-mortem examinations were made at No. 5 General Hospital by one of us (S. W. P.); and the bacteriological work was carried out in the laboratory of No. 25 Stationary Hospital by the other two (E. M. L. and F. E. W.).

NOTE ON THE PREPARATION OF MEDIA FOR THE CULTIVATION AND STUDY OF *B. INFLUENZAE*.

The experiments described below were carried out towards the end of 1918, when the epidemic of influenza, which had been prevalent, was subsiding.

In the previous epidemic, in June 1918, during which some fifty cases of influenza were investigated in this laboratory by Lieutenant-Colonel C. J. Martin, F.R.S., A.A.M.C., the medium used for the isolation of *B. influenzae* consisted of agar to which unheated citrated rabbit's blood had been added. A suitable piece of tracheal mucus was selected, washed in saline or water, and sown on rabbit's blood-agar plates and incubated for eighteen to twenty-four hours at 37° C. On this medium *B. influenzae* appeared as very small, hemispherical, perfectly clear colonies. After a little practice in the preparation and use of this medium, little difficulty was experienced in growing *B. influenzae* from sputum from patients suffering from the disease.

When the second wave of the epidemic began in this Base in the autumn of 1918, a similar technique was adopted in order to cultivate, if possible, *B. influenzae* from sputum, and from autopsy material from influenza cases. In the earlier stages of our observations at this time we found that we were not so successful in isolating the organism as in June. Frequently we failed to obtain a growth of the bacillus from material which, as microscopical examination of stained smears showed, contained minute gram-negative bacilli, morphologically resembling the influenza bacillus of Pfeiffer, in great numbers ; and, moreover, when colonies of *B. influenzae* developed on our plates they were usually few in number. The one point of difference which had been introduced into the technique was that whereas in June rabbit's blood was used exclusively, in these earlier experiments, which met with only a limited success, we used human blood. Our earliest experiments were made with blood, and blood-agar, which had been supplied to us from the pathological laboratory of a venereal diseases hospital, the blood having been obtained from patients. This medium, although excellent for the cultivation of other organisms, was found to be of little value for the cultivation of *B. influenzae*. We thought, at the time, that possibly the fact that some of the patients had received intravenous injections of salvarsan might account for the small success we met with when using the medium, but we found later that no better results were obtained when blood from healthy, normal human beings was used. We then returned to the original method of June, as used by Martin, and used citrated rabbit's blood and encountered no further difficulty in isolating *B. influenzae* from our material.

It appears, therefore, that in isolating *B. influenzae* the species of animal from which the blood required for the media is derived is a factor of some importance, and may possibly account for the failure which some workers have experienced to isolate *B. influenzae* from material which microscopical examination shows to be heavily infected with the organism. A series of experiments was therefore carried out with a view to studying this, and two other, points.

It was suggested to us that the addition of potato extract had been of value in the isolation and cultivation of the gonococcus and certain other organisms, and that the addition of potato extract to our blood-agar might provide a medium suitable for our purpose. This was tried.

It has been known for some years that media containing *heated* blood yields more profuse growths of *B. influenzae* than similar media containing *unheated* blood. The earlier observations on this point have been repeatedly confirmed, and quite recently media containing ' changed ' blood have been prepared and studied in greater detail by Fleming, Levinthal, and Matthews.

The following batches of media were made, and their value for the isolation and cultivation of *B. influenzae* studied and compared.

(i)	Agar	and	unheated	citrated	human blood
(ii)	,,	,,	,,	,,	rabbit's ,,
(iii)	,,	,,	,,	,,	horse ,,
(iv)	,,	,,	,,	,,	human blood and potato extract.
(v)	,,	,,	,,	,,	rabbit's ,, ,, ,, ,,
(vi)	,,	,,	,,	,,	horse ,, ,, ,, ,,
(vii)	,,	,,	heated	,,	human blood
(viii)	,,	,,	,,	,,	rabbit's ,,
(ix)	,,	,,	,,	,,	horse ,,
(x)	,,	,,	,,	,,	human blood and potato extract
(xi)	,,	,,	,,	,,	rabbit's ,, ,, ,, ,,
(xii)	,,	,,	,,	,,	horse ,, ,, ,, ,,

The media containing the heated blood (Nos. vii–xii) was prepared in the following way. Tubes containing 5 c.c. of nutrient agar were melted and allowed to cool to 60° C. and 0·2 c.c. of citrated blood added to each tube, the tube shaken gently to secure a homogeneous mixture, and then transferred to another bath at 80° C., and left there for a few minutes until the contents of the tube became chocolate in colour. The tubes were then sloped. In preparing the media containing the so-called ' unheated ' blood the melted agar was cooled to 50° C. and the citrated blood added and the tubes sloped at once. This latter medium is of a bright red colour.

On the twelve varieties of media thus prepared the growth of ten strains of *B. influenzae* was studied. The results of our observations are summarized below.

(i) *B. influenzae* grows much more profusely on media containing blood which has been heated to 80° C., and the colonies which develop on such heated blood-agar are invariably larger than those which grow on unheated blood-agar.

(ii) A better growth is obtained on media containing unheated rabbit's blood than on media containing unheated horse blood, and this latter yields better growth than media containing unheated human blood. In six of the ten strains studied no growth occurred on the unheated human blood-agar media, and the growth on the remaining four cases was extremely scanty. Three out of the ten strains failed to grow on the unheated horse blood-agar, and growth was obtained in nine out of the ten strains sown on to unheated rabbit's blood-agar. In the corresponding media containing heated blood, a good growth was obtained in nearly every case.

(iii) The addition of potato extract did not affect in any way the cultural value of the various blood-media tested.

(iv) On numerous occasions we observed that strains of *B. influenzae* cultivated on media containing unheated blood, on examination showed bacilli of the filamentous variety. Subcultures of these involution forms on to heated blood-agar media resulted in a growth of organisms morphologically true to type.

In this laboratory we make use of media containing either unheated or heated blood, according as to whether (i) sputum or autopsy material is being examined for the presence of *B. influenzae*, or whether (ii) a previously isolated and identified strain of *B. influenzae* is being dealt with. It is now our practice to sow sputum or other material on plates of unheated rabbit's blood-agar. The blood being added to the melted agar at a relatively low temperature (50° C.), such plates have a bright red appearance, and the unchanged haemoglobin which they contain serves as a valuable 'indicator', and is an aid to the picking off of colonies of *B. influenzae*, and to the differentiation of them from colonies of pneumococci and haemolytic streptococci. If, on the other hand, a large quantity of influenza organisms is required (e. g. for the preparation of vaccines, for the study of the agglutination reaction, &c.), we use media containing 'changed' blood, as on these media colonies are much larger and growth is more profuse. When using heated blood there is not much to choose between the rabbit and the horse, but with human blood the results are not quite so good; in our experience Levinthal's medium or Matthew's medium are even better.

We have also carried out experiments in order to discover, if possible, a medium which will preserve the bacillus of influenza in a viable condition for some time. We find that the following medium keeps the bacillus alive for a period of sixteen days, and twelve out of fifteen strains were found to be still alive when examined twenty-one days after inoculation. The basis of this medium is nutrient agar containing 2 per cent. of starch: this is tubed in 5 c.c. quantities, melted, and cooled to 60° C. To each tube 0·2 c.c. of citrated blood (the species of animal from which the blood is drawn is immaterial) is added, the whole gently shaken and immersed for a few minutes in a bath at 80° C., until the contents become chocolate in colour. The tubes are then put into a rack and allowed to cool in an upright position. The tubes are inoculated with two or three stabs, incubated for twenty-four hours at 37° C., and the plugs then paraffined and the tubes returned to the incubator, where they are kept.

6. REPORT ON THE MORBID ANATOMY OF INFLUENZA

BY

T. H. G. Shore, M.B. (Cantab.), M.R.C.P. (Lond.)
Temp. Capt. R.A.M.C.

(From the Central Mortuary, Étaples Base.)

The present remarks concern the autopsies on a series of 143 cases dying from influenza or its complications during October and November, 1918. It is much regretted that more were not examined, but during the height of the epidemic it was not possible to examine more than one in three or four.

It was originally intended that Captain W. Rolland, R.A.M.C., should investigate the bacteriology of the post-mortem material, and in a great many cases he did, but his early recall to civil life has put an end to his work. It may be possible to publish his work later, together with some detailed histology of the lesions described below.

I. General Considerations.

The striking features revealed by these post-mortems are three:

The constancy of pulmonary lesions.
The constancy of myocardial changes.
The frequent occurrence of haemorrhages.

Very varying amounts of pneumonia were found, and often the amount seemed quite inadequate as a cause of death, but the myocardial condition was hardly ever such as easily to be overlooked, and amply compensated for the small amount of pneumonia. The presence of haemorrhage in various situations, and notably in the lungs, is probably evidence of a widespread and severe toxaemia.

Comparatively few of these fatal cases could be regarded as below the average in physique, and most were robust and apparently previously healthy men.

Apart from the disease itself the chief debilitating factor was tuberculosis, and that did appear to be present in a higher proportion of cases than previously found. In this series it occurred in twenty-one cases or 14·7 per cent. (the proportion was 9·6 per cent. in a previous series of 1,500 cases, chiefly dying from wounds). In 10 cases the lesion was pulmonary, but active in only 2. Glandular tuberculosis was present in 11, the abdominal and thoracic glands being involved in about equal numbers.

One patient had been poisoned by phosgene and another by 'mustard' gas, and two were suffering from slight wounds of the limbs. Acute appendicitis was found in one, and chronic bronchiectasis in another. Nephritis older than the present disease was found in five cases.

The morbid anatomy of these cases is best described under the following regional headings: lesions found in the pleura, lungs, mediastinal glands, heart, liver, spleen, kidneys, and brain, and a few other lesions not admitting of a grouped classification.

II. Lesions Found in the Pleura.

Pleurisy was found as follows:

	Old.	*Old, assoc. with T.B.*	*Recent.*	*Serous Effusion.*	*Empyema.*
Bilateral . .	5	4	57	8	4
Left . . .	11	4	18	6	9
Right . . .	21	7	20	3	3
Total . .	37	15	95	17	16
		Included in previous column.		Included in the previous column.	

Total effusions (serous and purulent) = 33, or about one in three of all recent pleurisy.

The old pleurisy was met with chiefly in the form of adhesions over the lower lobe—a few cases showed apical adhesions only, or were universal.

Recent pleurisy was found—usually dry—over the lower lobes and behind, often extending over the upper lobe, but seldom much in front of the mid-axillary line. A certain amount of lymph exudate was commonly seen on the surface of the lung. The parietal pleura almost always showed vascular dilatation and roughening of the surface when visceral pleurisy was present.

Effusions were generally small—viz. half to one pint—in the case of serous effusions, and up to over two pints in one case of empyema. Clear effusions were, no doubt, in some cases referable to cardiac failure, for it was not uncommon to find them associated with absence of dullness of the lung surface.

Haemorrhagic effusions were seldom seen, and never in marked degree.

III. Lesions of the Lung.

Conditions ranging from profuse oedema to lobar consolidation have been found in the lung. Whatever else was found, oedema was one of the prominent features, and the oedema was of a peculiarly slimy character in many cases in which the consolidation was extensive.

The types of pneumonia found may be classified as follows and considered separately:

A. Haemorrhages and haemorrhagic pneumonia.
B. Broncho-pneumonia—or capillary bronchitis.
C. Miliary pneumonia or bronchiolitis.
D. Lobar pneumonia.

A. *Haemorrhage and Haemorrhagic Pneumonia.*

In most cases broncho-pneumonia was accompanied by haemorrhage, present either as small round subpleural petechiae scattered over

the surface of a lobe and roughly proportional in amount to the degree of consolidation, or as larger masses of interstitial haemorrhage, which closely resembled red infarcts when near the surface of the lung. The latter type has been observed to follow the line of a vessel as if produced by leakage from various points along its course.

Broncho-pneumonic patches have often been found surrounded by a zone of the more usual consolidation—suggesting that the haemorrhage preceded the consolidation and provided pabulum for the rapid growth of organisms. (Organisms of a haemoglobinophilic type, such as Pfeiffer's bacillus, readily grow in such surroundings.)

Further, cases of death after short illness were more prone to show obvious haemorrhage than those of longer standing. A very characteristic type of lesion was one in which the lung was bulky from emphysema, and showed numerous plum-coloured haemorrhagic areas, varying in size from the size of a shilling up to a third of the lower lobe—the latter being produced by coalescence of smaller areas.

Discrete lesions resembled infarcts on section, and seen through the pleura were often of polygonal shape. They were quite solid, and on microscopic section were clearly due to haemorrhage. There was no obvious cause for infarction in these cases, and, though no microscopic evidence is adduced, were probably due to leakage from vessels the walls of which were unduly permeable.

This condition was present in early cases, and in cases showing the more profound toxaemia. In a few cases watched clinically haemoptyses were found from time to time. These were the cases which most constantly showed the presence of influenza bacilli—both in the sputum and in cultures made from the lung post-mortem.

B. *Broncho-pneumonia.*

Broncho-pneumonic areas of greater or smaller extent were the most common pulmonary post-mortem finding. They tended to coalesce, and generally there was compensatory emphysema, most often seen in the anterior parts of the lobes, but a finer mixture of emphysema, consolidation, and collapse was often seen, as in the broncho-pneumonia or capillary bronchitis of children. Sometimes it was hard to distinguish in these cases between confluent broncho-pneumonia and lobar pneumonia, but probably the latter was not common. In a fair proportion of cases of broncho-pneumonia necrosis of the lung was present, generally of small areas, but occasionally these were found to have blended into extensive branching abscesses. Almost all cases showed pus in the bronchi, and on section small beads of pus oozed from the finer tubes. This was not found in consolidated areas only, but occurred in what otherwise seemed to be fairly normal lung, recalling the purulent bronchitis of two years ago. (*Lancet*, 1917, ii, 41.)

The trachea was quite often much injected, especially in its lower part, and occasionally a slight membrane or pseudomembrane was found partially detached, but much more often there was a slimy mucopurulent secretion which welled up from the main bronchi. The injection was seldom extremely marked as in poisoning by gas or other respiratory irritants, and seldom extended much above

the larynx, although in some cases the fauces and pharynx were markedly involved. Injection was most prominent in haemorrhagic cases.

Altogether broncho-pneumonia was present in 113 cases. In 77 excessive oedema was noted; 48 showed marked purulent bronchitis, and in 51 compensatory emphysema was prominent.

Necrosis or abscess of the lung occurred 12 times; in 4 it was the obvious origin of empyemata, but in 2 there was no pleurisy, as the areas of consolidation involved were deeply situated.

The figures just given include also those under the heading of haemorrhagic pneumonia, as the possibility of separate consideration of these cases did not become apparent until too late to place them in a category by themselves. Interstitial haemorrhages and subpleural petechiae were noted as follows:

Interstitial haemorrhage	68
Subpleural petechiae	54
Both	24

Of 12 cases of necrosis of the lung haemorrhage was found in 10.

C. *Miliary Pneumonia.*

This type of pneumonia was fairly often found, and is associated with plugging of bronchioles with pus and fibrinous exudate. A small area of consolidation, with leucocytes, epithelial cells, and fibrin in the exudate, forms around the affected tube, and gives rise to a very characteristic macroscopic condition, which, however, is much more easily felt than seen. When the lung is handled it reminds one of a bag of peas, each nodule feeling rather smaller than a pea, and the surrounding lung quite soft and non-resistant. This condition is generally called bronchiolitis, but as definite consolidation of the lung is present, the name miliary pneumonia seems more appropriate.

Miliary pneumonia was found in twenty cases—14 per cent. of all cases or 18 per cent. of all broncho-pneumonia. It occurred as described in discrete form in twelve cases, and in a condition of becoming confluent into larger areas, or associated with ordinary broncho-pneumonia, in the remaining eight. Thirteen cases showed haemorrhage, eleven showed a marked degree of emphysema, and pleurisy was present in thirteen. Bilateral in eleven. Two small empyemata were found in cases of miliary pneumonia.

It was thought that this type of pneumonia might be more definitely associated with the presence of Pfeiffer's bacillus than the more normal broncho-pneumonia, because of its obvious relationship to purulent bronchitis, but this bacillus was not constantly found. Pneumococci and streptococci were found as frequently.

D. *Lobar Pneumonia.*

The lobar distribution of consolidation was not common. It was found in fifteen cases, which may be subdivided as follows:

(*a*) Almost certainly confluent broncho-pneumonia .	7
(*b*) Showing broncho-pneumonia of the other lung .	4
(*c*) Probably true lobar pneumonia	4

Only two showed empyemata—both of type *b*. Three showed serous effusions (all left-sided)—two belonged to type *b*, and one to type *c*, the latter being a very small effusion, and turbid, though not obviously purulent.

Consolidation was always present in the grey stage though a few cases showed some areas of consolidation of more recent date, especially in the upper lobes.

The cut surface of these lungs constantly showed a very wet and slimy condition, and was not of such a granular or 'ground glass' appearance as is found in typical lobar pneumonia.

A large amount of oedema was also present in seventy-seven cases of broncho-pneumonia, and in five it was the only pulmonary lesion found.

IV. Lesions of Mediastinal Glands.

Enlargement of glands at the roots of the lungs and around the lower end of the trachea was very often found, and more often during the latter part of the investigation than at first—probably because they were more frequently examined. Altogether they were found to be affected in ninety-one cases, of which twenty occurred in the first forty-three and seventy-one in the final hundred. In all probability 75 per cent. is near to the actual proportion in which they were involved.

These glands, and in a few cases the abdominal, inguinal, and cervical glands, showed much swelling due to congestion. In some cases this was absent, and the glands were pale, soft, and even breaking down, especially when there was a necrotic patch in the lung.

It is possible that the enlargement of these glands accounts for the clinical observation of a cough closely resembling whooping cough—namely a series of expirations followed by a single inspiration, in repeated spasms and in a few cases ending in a small vomit. This has been observed many times, and the state of the mediastinal glands found post-mortem suggests a causation similar to that of the cough met with in children affected by tuberculosis of these glands.

V. Lesions of the Heart.

It was very unusual to find a heart in these cases of influenza death that could be considered normal. Dilatation of the right side was the rule, and of the left extremely common. The myocardium was generally paler than usual, often showed early fatty change, and was almost always soft. Sections in the fresh state stained with Soudan III showed intense fatty degeneration. The condition of the heart muscle fully bears out the clinical observation of low blood pressure. It would be curious if such hearts could sustain a normal intraventricular pressure. The blood pressures of a ward of thirty-five patients, all in the first week of the disease, gave an average of 93 mm. Hg, the lowest being 84 mm. (taken by a dial instrument, and checked by normal controls). The pressure was found lowest at about the third or fourth day and in severe cases took several

weeks to recover. Unfortunately the pressure just before death was not taken in any of these cases. In two cases of post-influenzal depression or psychasthenia the pressure was 10 mm. below normal as much as eight weeks after the attack of influenza.

Dilatation was found in 138 cases. Myocardial pallor or softening or both in 135 cases.

In many cases the endocardial half of the muscle was very noticeably paler than the outer half. This was much more marked in some cases than in others, and was found especially in early fatal cases, and in those showing the greatest dilatation. The reason is presumably to be found in the vascular supply to the heart muscle—the smaller branches of the coronary arteries being furthest from the vessels' origin on the outside of the heart, and the part supplied by them on the inner side most affected.

The heart, like the lungs, showed subserous haemorrhages, but by no means so commonly. They were noticed in sixteen cases, in the form of small discrete rounded subpericardial haemorrhages. Occasionally small endocardial haemorrhages of a similar type were found, but with a tendency to be more irregular, or flame shaped, resembling those found in the retina in other conditions.

Pericarditis and endocarditis were not found at all. The average heart weight was 12 oz. The largest 16 oz. and the smallest 8 oz.

VI. Lesions of the Liver.

In most cases there was found some fatty change in the liver, often taking the form of irregular areas, visible beneath the capsule, and on section, of yellowish colour, and surrounded by normal looking liver. In some cases the whole liver was pale and very obviously fatty-enlarged, and with a rounded instead of a sharp anterior edge. In some cases the left lobe seemed more affected than the right, but usually they were affected equally.

In a considerable number congestion was present—doubtless accompanying a gradually failing heart, and when present together a 'nutmeg' appearance was produced.

Nothing abnormal was noticed in the gall bladder or bile ducts. Fatty change in the liver was found in 130 cases, congestion in forty-nine cases, and both were present in thirty-eight cases.

The average liver weight was 68 oz.—the largest being 109 oz. and the smallest 41 oz.

Jaundice of a non-obstructive type was found in five cases. These all showed evidences of severe toxaemia. Jaundice was not deep in any of them.

VII. Lesions of the Spleen.

The condition of the spleen is always very difficult to describe. but two main types can be mentioned in this series of cases apart from congestion, which may be present as well.

(1) The malpighian bodies may stand out prominently on cut section, as in the 'sago' spleen, the rest of the organ being either pale or congested, which latter makes the pallor of these bodies

more apparent. The spleen is usually enlarged, flabby, and often very soft. When not congested the capsule is often wrinkled.

(2) The spleen as a whole may be pale and flabby—not soft—the consistence reminding one rather more of gelatin or india rubber. It is not nearly so friable as the preceding type, and on section presents a much more uniform appearance. The malpighian bodies do not appear enlarged, and need looking for. The organ is just as often enlarged as the preceding. Enlarged malpighian bodies were found in forty-five cases, the pale flabby spleen in sixty-eight cases, and congestion was present in fifty-eight cases.

The average spleen weight was 6·6 oz. The largest spleen weighed 19 oz. and the smallest 3½ oz.

VIII. Lesions of the Kidney.

Macroscopically the kidneys almost always showed some changes which were probably attributable to the action of toxins passing through them. On the average they were a little larger than usual, and were certainly paler and softer.

Generally the cortex was a little swollen, and there were streaks, indicating areas of congestion, upon a pale or yellowish background. The bloody kidney of acute nephritis was never seen. The medulla was of a darker colour, and often showed marked congestion. The capsule stripped off easily, with a few exceptions where there was nephritis of longer standing, and the surface exposed showed distended stellate veins upon a pale smooth background. The renal substance was often quite friable. These are the appearances of what might be termed the ' toxic ' kidney, and were present in 130 cases.

Microscopical sections showed lesions which fall in line with the gross morbid anatomy.

Glomeruli were not involved except for some terminal congestion. The brunt of the damage was borne by the tubules—and especially the convoluted tubes and ascending limb of the loop of Henle. These showed desquamation with epithelial casts in situ, and in several cases a great deal of fatty degeneration was present. Hyaline was constant in the few cases it was possible to examine at the time.

About fifty cases showed, either in addition to the toxic state or apart from it, a considerable amount of congestion, which is not surprising as a result of failure of the right side of the heart.

Subacute or chronic nephritis—probably of much older date than the terminal influenza—was found in five cases only, and in all it was of the glomerulo-tubal type. The granular kidney was not seen.

Haemorrhage under the mucous membrane of the renal pelvis was seen three times, in the form of small closely crowded points as large as a pin head.

The average kidney weight was greater than normal—12·3 oz. the pair.

Oedema of the extremities, hydrothorax, ascites, or lumbar oedema were not seen except in one case of subacute nephritis, in which a small hydrothorax was found.

IX. Lesions of the Brain.

The brain was only examined in twenty-two cases and in those because some special cerebral symptoms were present.

The conditions found were as follows :

Meningeal oedema	11
Great congestion	3
Encephalitis	2
Meningitis	2
Hydrocephalus	1
Natural	3

The degree of oedema was often high and well in agreement with the condition of meningism from which the patients suffered.

Encephalitis was present in two cases and showed itself as multiple punctate haemorrhages studded throughout the white matter of the cerebrum, basal ganglia, pons, medulla, and cerebellum. The grey matter appeared not to be affected. The individual haemorrhages were small, but varied somewhat in size, and in some places were noticeably more abundant than in others ; collections were especially seen near the posterior end of the corpus callosum. As only two cases were examined no generalizations are possible, but the constant affection of the white matter is remarkable. The condition most nearly resembling what was seen is the state of the brain in poisoning by phosgene gas.

The two cases of meningitis showed no influenza bacilli on culture. One was caused by the meningococcus, and the other by the pneumococcus. The condition was in no way remarkable.

In one case in which headache had been a very prominent symptom inflammation of the frontal sinuses was found and the influenza bacillus found in the pus they contained.

A moderate degree of acute internal hydrocephalus was found in one case. No cause for this was found, the base of the brain appearing clear—meningitis was absent. During the last few hours of life this patient had a persistent spontaneous clonus of the right leg below the knee, but no localizing cerebral lesion was found.

X. Other Post-mortem Findings.

Haemorrhages have been found in other situations than those mentioned—the lungs, heart, and brain.

The lowest segment of the rectus abdominis muscle was haemorrhagic in eleven cases. At first excessive coughing was thought to be a possible cause of this, but a section cut by Captain Bashford, R.A.M.C., showed that an extensive myositis was present, with degeneration of the myelin, and proliferation of the sarcolemma cells.

Mesenteric haemorrhages were noticed once.

Intestinal haemorrhage occurred twice, and haemorrhage in the stomach once.

A gross haemorrhage into the tissue of the spleen was seen once.

Parotitis was seen in one case—associated with encephalitis. The bacteriology of this case was not worked out, but the association

of these two conditions reminds one of the cases found by Gordon in children. (L. G. B. Reports, No. 96 (New Series), 1914.)

Enteritis is probably fairly common, but was not often looked for. Injection of the mucous membrane of the colon was found in a fair number of cases, but records were not sufficiently kept to give figures on this point.

The work done by Captain W. Rolland, R.A.M.C., upon the bacteriology of this disease tends to show that the lesion most associated with the influenza bacillus is the haemorrhage, especially the haemorrhagic stage of pneumonia. When cultures were made from the infarct-like areas Pfeiffer's bacillus was found in nearly every case, and generally in almost pure culture. The same applied to the clinical aspect of the same condition. When the first haemoptysis was noticed, the influenza bacillus was easily recovered from the sputum.

Glands proved sterile on culture.

Effusions did not yield the bacillus—the usual organism in empyemata being the pneumococcus.

Blood cultures were always sterile.

Whatever the true bacteriology of influenza may be, there appears to be a fairly clear post-mortem picture associated with the activities of Pfeiffer's bacillus in this epidemic.

The most characteristic lesion is haemorrhage.

The most fatal lesion is probably myocarditis, and evidences of the extreme toxaemia are further to be found in the fatty liver and kidneys, and the enlarged spleen—and possibly meningeal oedema.

Enlargement of lymphatic glands was most marked in the thorax, where other toxins were at work in the lungs, so that this lesion can hardly be regarded as influenzal only.

Haemorrhage appears to take place in the lung, and in its immediate neighbourhood Pfeiffer's bacillus is found. Secondary infection leads to broncho-pneumonia which may be caused by a variety of organisms, prominent among which are the pneumococcus and a streptococcus. These are organisms commonly found in the respiratory passages, and multiply rapidly in the haemorrhagic pabulum the influenza bacillus has set free. Probably the influenza bacillus remains local, forming toxins which, carried over the body, produce the cardiac, hepatic, and renal lesions. No more than degenerative lesions are found elsewhere, such as a toxin, rather than an organism, would produce. The appearances described above may all be secondary to some other infection, but are nevertheless mainly caused by the influenza bacillus.

The type of pneumonia referred to as miliary pneumonia is due to extension of inflammation from the bronchioles into the neighbouring alveoli, and is not as a rule associated with haemorrhage. The pathology is probably not the same as in the more characteristically influenzal lesions.

7. REPORT ON PNEUMONIA FOLLOWING INFLUENZA

BY

Captain A. V. Bock, Med. Corps, U.S.A.
AND
Captain J. L. Stoddard, Med. Corps, U.S.A.
(From the Laboratory, No. 13 General Hospital.)

I. Material.

1. *Number of Cases.* 39 cases of severe pulmonary complications in the course of influenza.
2. *Classification of Cases.* 25 Lobar Pneumonia; 14 Bronchopneumonia.
3. *Nationality.* 14 of the cases were British; 25 American.
4. *Source.* 12 field hospitals and casualty clearing stations.
5. *Season.* November 1918.

II. Methods.

1. *Clinical.*
   (*a*) *Isolation* in a special ward as soon as pneumonia diagnosed. Beds separated by hanging sheets. White gowns and gauze face masks used.
   (*b*) *Blood Cultures.* Done as soon as possible after admission on nearly every case. 6–10 c.c. of blood in 50 c.c. 1 per cent. glucose bouillon.
   (*c*) *Sputa.* Examination: (1) Stained smears. (2) Attempting to isolate the pneumococcus by the Avery method.
2. *Post-mortem.* Examinations in all fatal cases.

III. Lobar Pneumonia.

1. *Clinical Findings.*
   (*a*) *Mortality.* Of 25 cases, 17 died and 8 lived.
   (*b*) *Lobes consolidated—Surviving Cases* (8). Right lower lobe 5, both lower 1, right lower and right upper 1, both lower and right upper 1.
   Fatal cases (17). Right lower 1, left lower 4, both lower 6, both lower and right upper 1, both lower and left upper 1, left lower and left upper 1, right lower and right upper 1. In the two remaining cases there were signs of consolidation in one side, and diffuse bronchopneumonic signs in the other.
   (*c*) *Temperature*, 102–105°.
   (*d*) *Recovery.* Crisis in one case. In seven lysis.
   (*e*) *Sputum.* Tenacious, blood tinged.
   (*f*) *Average Duration.* Fatal cases, 12 days; surviving, 9.

IV. Broncho-Pneumonia.

1. *Clinical Findings.*
   (*a*) *Mortality.* Of 14 cases, 11 died and 3 recovered.
   (*b*) *Lung Signs.* Great daily variations, often absence of pathological signs. Suppressed breathing at the bases, moist consonating rales, and patches of bronchial breathing in the interscapular spaces were common. In a few cases signs of consolidation in one or both lower lobes before death (the confluent cases).
   (*c*) *Temperature.* Great diurnal variations. Average lower than in lobar cases.
   (*d*) *Sputum.* Characteristic of influenza, pale-green, numular, with mucous *B. Influenzae.* In only 2 cases pneumococci grown.
   (*e*) *Average Duration.* Fatal cases, 15 days; surviving, 17.

V. Blood Cultures.

The Results are shown in Table I.

	Number Positive.	*Number Negative.*	*Per cent. Positive.*	*Per cent. Negative.*
Lobar Pneumonia	13	9	59	41
Broncho-Pneumonia	0	11	0	100

The pneumococcus was identified by the following characteristics:
(*a*) Greenish colour in blood bouillon.
(*b*) Diffuse cloudiness in bouillon with no flocculent precipitate and very little settling.
(*c*) Pneumococcus-like colonies on blood agar.
(*d*) Bile solubility (not always tested).
(*e*) Typing with sera furnished by the Rockefeller Institute. The types are shown in Table II.

	Type 1.	*Type* 2.	*Type* 4.
Number of Cases . . .	1	11	1

Table III.

Average number of days before death at time of cultures, and temperature at time of culture.

	Days.		*Temperature.*	
	Positive Culture.	*Negative. Culture.*	*Positive Culture.*	*Negative Culture.*
Lobar Pneumonia	2·9	1·5	103·6	104·5
Broncho-Pneumonia	0	3·7	—	102

Seven cases of lobar pneumonia in which blood cultures were negative or were not done were typed by isolating the pneumococcus from the sputum by the Avery method, or by culture obtained from lung puncture. These showed four cases of type 2, and three of type 4 pneumococcus. In 20 cases of lobar pneumonia, therefore, the types of pneumococcus occurred as follows: type 1, one case; type 2, fifteen cases; type 4, four cases. In no case was type 3 recovered.

In cases having broncho-pneumonia the pneumococcus was isolated from the sputum in two cases only, one type 2 and one type 4—both fatal cases. Repeated attempts to grow the pneumo-

coccus in the other cases failed. Often few or none of these organisms could be seen in stained spreads of the sputum. The bacillus of influenza was found in the sputum of all the cases of broncho-pneumonia.

TABLE IV.

Mortality with reference to Positive Blood Cultures.

	Of Cases with Positive Cultures.		*Of Cases with Negative Cultures.*	
	Number.	*Per cent.*	*Number.*	*Per cent.*
Living . . .	1	7·7	6	66
Dying . . .	12	92·3	3	33

VI. PATHOLOGY.

Pathological Findings. The gross appearance of pneumonic lungs suggests a division into the following groups :

(1) *Pure broncho-pneumonia.* The lesions are discrete with definite limits. Pleurisy is not often concurrent.

(2) *Rapidly spreading broncho-pneumonia.* The patches are large and ill-defined, often becoming confluent. Even when a whole lobe is involved in a confluent process, it does not have the massive appearance of true lobar pneumonia and an unevenness is evident on palpation and section. Usually there is no pleurisy ; if present it is of the dry kind. Two cases in our series were of this type.

(3) *Pure lobar pneumonia.* The lungs are typical. They are large, massive, and evenly firm on palpation. In distinction to the two previous types there is almost invariably a marked fibrino-purulent pleurisy over the affected lobe. This pleural lesion is lacking over other lobes in the same case, which are not involved in the lobar process, even though they have marked broncho-pneumonia.

The cut surface shows even consolidation, some in the stage of red hepatization, some in the grey stage.

(4) In a certain number of cases the lobar pneumonias give evidence of a previous broncho-pneumonic process in the same lobe. Immediately about the bronchi there are areas showing older, harder lesions, of a red or grey colour.

(5) In many cases the lobes not involved in the lobar process show a broncho-pneumonic process. It is quite probable that in some of these cases there is also a broncho-pneumonic process in the lobe with lobar pneumonia, which is obscured by the lobar consolidation.

(6) In three cases a lobe or lobes are oedematous, with red fluid, and airless, but not consolidated.

Associated processes. Marked bronchitis is nearly always present. Pericarditis is noted in three cases. In one case it is of the dry adhesive type, and concurrent with broncho-pneumonia. In the two other cases it is purulent and associated with lobar pneumonia. The pericardial exudate contains a pure culture of pneumococcus in each of the two latter cases. In one case the pneumococcus, on typing, proves to be type 2, the same type as in the blood culture and lung culture.

Empyema. In four cases empyema occurred with lobar pneumonia, in one case with broncho-pneumonia. Marked collapse occurred only in the broncho-pneumonic case.

Pleural exudate. In six cases, all lobar pneumonia, there was excess of pleural fluid, slightly cloudy, and reddish-brown.

8. ON THE AGGLUTINATION OF *B. INFLUENZAE* (PFEIFFER) BY THE SERUM OF PATIENTS SUFFERING FROM INFLUENZA.

By Captain P. Hartley, R.A.M.C., T.F.

(From the Laboratory, No. 25 Stationary Hospital, B.E.F.)

During the recent epidemic, at the end of 1918, the opportunity occurred for testing the sera of patients who were suffering from influenza for agglutinins to *B. influenzae*. It was thought that investigations on these lines might throw some light on the vexed and still unsettled question of the part which Pfeiffer's bacillus of influenza plays in the disease. The epidemic subsided rather quickly in this Base and in consequence some projected experiments were left unfinished. The results which have been obtained up to the present are set out briefly below.

I. Material Used.

The first material which became available was serum obtained from the heart blood taken at autopsy on cases of influenza. In all, twenty-one satisfactory samples of serum were obtained and examined. They were supplied by Major S. W. Patterson, R.A.M.C., Pathologist, No. 5 General Hospital, who, with Little and Williams of this hospital, was investigating at the time a series of cases of influenza. These workers investigated fifty-six cases and demonstrated the presence of *B. influenzae* (Pfeiffer) in the lung or bronchus of every case except one. The next material studied consisted of serum from patients who ultimately recovered from the disease. It was hoped to be able to compare the agglutinin content of the serum of the same patient at different stages of the disease, but on account of lack of material this was only possible in one case.

II. Method.

A macroscopic method was used. The patient's serum was tested at dilutions of 1 in 50, 1 in 100, and 1 in 200 only. Equal volumes of diluted patient's serum and emulsion of *B. influenzae* were mixed in a small test tube, heated to 55° C. for three hours and read off from fifteen to thirty minutes after removal from the bath. The racks were left on the bench until the following morning when a second reading was made. In each experiment, when a number of patients' sera were being tested, at least three and sometimes five samples of normal sera were set up and tested in precisely the same way.

III. The Emulsions of *B. Influenzae* Used.

As some unexpected difficulties were encountered in the earlier experiments the following notes may be of interest, and perhaps of some use, to other workers on this subject.

Eight strains of *B. influenzae* were used ; seven had been isolated from the lung and one from sputum. In the earlier experiments the organism was grown on unheated rabbit's blood-agar, on plates which were inoculated from a pure culture by making a series of parallel strokes. The plates were incubated for eighteen to twenty-four hours at 37° C., a number of colonies picked off and examined, and if found satisfactory the growth was taken off with a platinum loop and emulsified in a measured quantity of saline and diluted if necessary. A unit volume of this emulsion was then heated to 55° C. for three hours, and if the suspension remained perfectly uniform and unagglutinated the tests with diluted patient's serum were proceeded with.

These precautions are necessary as it was found that different strains of *B. influenzae* exhibit very varying degrees of 'auto-agglutinability'. Some strains agglutinate after standing on the bench for about an hour, others are stable at room temperature but agglutinate after heating at 55° C. for three hours, while others remain perfectly stable after heating at 55° C. even for twenty-four hours. Moreover, it was found that a strain of *B. influenzae* may yield a perfectly stable and satisfactory emulsion on one day, yet a few days later another generation of the same strain may yield an emulsion which agglutinates spontaneously at room temperature (strains 40 and 22 behaved in this way). The following observation was also made : A culture of strain 22 growing on unheated rabbit's blood-agar was examined and found to be typical. From this parent slope subcultures were made on two plates, one consisting of unheated rabbit's blood-agar and the other of heated (70° C.) rabbit's blood-agar. After incubation at 37° C. for eighteen hours each plate showed a good growth, but in neither case was the organism quite typical. The culture on the unheated rabbit's blood-agar showed long filamentous forms, while that on the heated rabbit's blood-agar yielded organisms which were a little longer than usual but otherwise typical. In the former case it was found to be very difficult to emulsify the growth in saline and the emulsion when made agglutinated on standing on the bench. In the latter case the growth emulsified easily, but spontaneous agglutination occurred at room temperature. Earlier in its history this strain had yielded emulsions which were perfectly stable, and since the above observation was made it has returned to normal habits.

At the time it was thought that the concentration of sodium chloride in which the bacilli were suspended was a factor affecting their agglutinability, but experiments showed that this was not the explanation. As a matter of convenience and routine the agglutination experiments described in this paper have all been carried out in a solution in which the concentration of sodium chloride was always the same in every tube, namely 0·5 per cent.

As a result of the later experiments, and other work on the bacillus of influenza, the very distinct impression has been gained that the blood used in making the media is a factor which affects the auto-agglutination of the emulsion as well as the morphological character of the organism. When using unheated blood one could never tell whether the resulting emulsion would serve for experimental purposes

or not. The emulsion had to be made, examined, and tested every time.

In the later experiments Matthew's medium was used and this was found to be perfectly satisfactory. Luxuriant growths were invariably obtained and these yielded stable emulsions of morphologically typical organisms.

IV. Summary of Results.

Series A. *Examination of twenty-one Samples of Serum from the Heart Blood of Fatal Cases of Influenza.*

In most cases the same sample of serum was tested against several strains of *B. influenzae* either on the same, or different, days.

Two readings of the tubes were made: the first from fifteen to thirty minutes after removal from the bath (the immediate reading), and the second on the following morning (the late reading). It was found that agglutination was sometimes observed after eighteen to twenty-four hours where none had been visible immediately after removal from the bath. 'Naked eye' agglutination was looked for throughout, no hand lens being used. In no case did any sample of normal serum agglutinate any strain of *B. influenzae* used, and all strains were tested before use for auto-agglutination and put up again with the sera during the tests. No strain used exhibited auto-agglutination.

The results obtained are set out below. The numbers refer to serial numbers given to patient's serum or to the strain used. The entry 'late' indicates that agglutination was not apparent after heating for three hours at 55° C., but was easily visible to the naked eye after standing at room temperature overnight.

Table I.

Patient's serum tested.	*Duration of illness.*	*Strains of B. influenzae tested.* (*a*) *Strains agglutinated by patient's serum.*	(*b*) *Strains not agglutinated by patient's serum.*
41	12 days	'Legge,' 'Hudson' (late), 40, 24, 45, 22, and 63	
42	6 ,,	'Legge,' 'Hudson' (late), 40, 24, 45, 22.	
53	11 ,,	'Legge,' 'Hudson' (late), 40, 22	
6	6 ,,	'Hudson,' 22, 40 (late), 63, 64	
8	8 ,,	'Hudson,' 24, 22	45
39	8 ,,	'Hudson,' 22, 63	40, 64
Freeman	? ,,	40, 63, 64	
35	17 ,,	40, 63, 64	
3	15 ,,	40, 63, 64	
40	10 ,,	'Legge,' 40	'Hudson'
52	10 ,,	24, 22	45, 40, 63, 64
7	11 ,,	63	
51	10 ,,	40 (late)	
25	8 ,,	'Hudson'	
36	8 ,,	63 (late)	40
34	13 ,,		40, 64
26	12 ,,		40
55	13 ,,		64
5	9 ,,		64
23	16 ,,		24, 45
24	10 ,,		24, 45

Table II.

The degree of agglutination is given in the two following summaries.

(*a*) *Immediate reading.*

Of the 21 sera examined,

7 agglutinated one or more strains of *B. influenzae* at 1/200.
5 „ „ „ „ „ „ „ 1/100.
1 „ „ „ „ „ „ „ 1/50.
8 failed to agglutinate the strains of *B. influenzae* against which they were tested.

(*b*) *Late reading.*

Of the 21 sera examined,

10 agglutinated one or more strains of *B. influenzae* at 1/200.
4 „ „ „ „ „ „ „ 1/100.
1 „ „ „ „ „ „ „ 1/50.
6 failed to agglutinate the strains of *B. influenzae* against which they were tested.

Table III.

Summary showing the Agglutination obtained with the Strains used.

Strains of B. influenzae used.	*No. of samples of sera against which tested.*	*No. of cases which gave,* (*a*) *Agglutination.*	(*b*) *No agglutination.*
'Legge'	4 cases	4	None
22	7 „	7	„
'Hudson'	8 „	7	1
63	9 „	8	1
24	6 „	4	2
45	6 „	2	4
40	14 „	9	5
64	9 „	4	5

Thus, nearly two-thirds of the sera tested agglutinated *B. influenzae* at a dilution of at least 1 in 50, and one-third of the cases agglutinated the bacillus at the relatively high dilution of 1 in 200. Unfortunately these were not tested out to ascertain their end point of agglutination.

The average duration of illness in this series was ten days.

Ten cases agglutinated all strains against which they were tested, and six failed to agglutinate any strain at the lowest dilution tested, viz. 1 in 50. Five sera agglutinated some strains and failed with others. This is an interesting point, and whether it indicates that there are serologically different types of *B. influenzae* is a matter for further investigation.

Series B. *The Agglutinin Content of the Serum of twenty Patients who ultimately recovered from Influenza.*

The average duration of illness in this series of twenty cases was seventeen days. Ten of the sera were tested against one strain of *B. influenzae* only, six were tested against two strains, and four against three strains.

Table IV.

(*a*) *Immediate reading.*

Of the 20 sera examined,

3 agglutinated one or more strains of *B. influenzae* at 1/200.
4 „ „ „ „ „ „ „ 1/100.
6 „ „ „ „ „ „ „ 1/50.
7 failed to agglutinate any strain of *B. influenzae* against which they were tested (4 of these 7 were tested against 2 strains, and 3 against 1 strain only).

(*b*) *Late reading.*

Of the 20 sera examined,
4 agglutinated one or more strains of *B. influenzae* at 1/200.
6 „ „ „ „ „ „ „ „ 1/100.
4 „ „ „ „ „ „ „ „ 1/50.
6 failed to agglutinate any strain of *B. influenzae* against which they were tested (4 of these 6 were tested against 2 strains and 2 against 1 strain only).

Comparing the two series A and B, although the numbers of sera tested are not great, the number of times that agglutination was observed was about the same in the two series, but agglutination occurred at a higher dilution in series A than in series B. In this connexion it is interesting to note that the serum was taken, on an average, ten days from the onset in series A, and, on an average, seventeen days from the onset in the case of series B.

Series C.

Unfortunately there is, as yet, only one completed observation in this series, the object of which was to study the agglutinin curve to *B. influenzae* in patients suffering from influenza.

In this case the first sample of serum was taken on the sixth day of the disease, and this agglutinated *B. influenzae* completely at 1 in 200 (immediate reading); a second sample was taken on the tenth day of the disease, and this agglutinated *B. influenzae* at 1 in 100 (immediate reading); a third sample was taken on the fifteenth day, and no agglutination was detectable by the naked eye at 1 in 50 at the immediate reading, but by next morning agglutination had occurred at this dilution. In making these agglutination tests the same strain of *B. influenzae* was used throughout.

V. Conclusions.

(i) The sera from forty-two cases were examined for the presence of agglutinins to *B. influenzae*, and it was found that twenty-seven of these agglutinated the bacillus at a dilution of at least 1 in 50.

(ii) The serum of normal healthy persons did not agglutinate the emulsions of *B. influenzae* used at a dilution of 1 in 50.

(iii) Evidence was obtained that agglutinins to *B. influenzae* are developed at an early stage of the disease and that there is a rapid decrease of these agglutinins during convalescence (cf. Fleming, *Lancet*, London, 1919, i. 139).

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VIII. THE EFFECTS OF DIMINISHED TENSION OF OXYGEN, WITH ESPECIAL REFERENCE TO THE ACTIVITY OF THE ADRENAL GLANDS

BY

C. H. Kellaway, M.C., M.D., M.S. (Melbourne), Major, A.A.M.C.
(From the Department of Biochemistry and Pharmacology, Medical Research Committee.)

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1. Introduction.

The development of aerial warfare has been associated with the recognition in flying officers of certain symptom-complexes which follow prolonged service flying, or may result from 'crashes' or other incidents accompanied by nervous stress. The best defined examples of these conditions are 'flying stress' and 'cardio-vascular debility'. In both the outstanding feature is a degree of instability, in the one case of the nervous, and in the other of the cardio-vascular system. Since these conditions occur in men flying at low as well as at high altitudes, and even in those engaged in war service other than flying, it is evident that nervous excitement must play an

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important part in their production. Evidence has, however, been accumulating to show that in airmen repeated exposure to want of oxygen, as suggested by Flack (1918), is a powerful adjuvant to nervous excitement. In men suffering from these forms of 'flying sickness' it was conceivable that this 'instability' might extend to the mechanism governing the activity of the suprarenal glands and that stimuli below the threshold of effectiveness in the normal individual might cause in them an increased output of adrenalin.

Hitherto there have been no direct observations upon the effect of anoxaemia in causing increased output of adrenalin. The work of Cannon and his co-workers (1916) established the fact that emotional excitement is one form of stimulus which operates in this way, though this has been recently denied by Stewart and Rogoff (1917 b); Cannon and Hoskins (1911), Elliot (1912) and Anrep (1912) showed that asphyxia also causes such an increased output, though this again has been called in question by Stewart and Rogoff (1917 a) and by Gley and Quinquaud (1918). Cannon has suggested a relation between the hyperglycaemia which results from emotional excitement and the increased output of adrenalin which occurs at the same time, and a similar relation has been supposed by some to exist in the case of asphyxia. According to Stewart and Rogoff (1917 b) no such relationship exists.

In all these investigations into the effect of asphyxia upon adrenalin output no attempt has been made to graduate the severity of the asphyxia, and for the most part the negative observations have been vitiated by the complicating effects of severe operative procedure under anaesthesia. It seemed desirable, therefore, to take up this question again, and, since there is no known satisfactory method of determining the presence of adrenalin in the peripheral blood of man, the observations have been made upon unanaesthetized cats, in which the preferential dilatation of the pupil, sensitized by previous removal of the corresponding superior cervical ganglion, has been used as an index of the output of adrenalin. This proved to be perfectly satisfactory as an index of the suprarenal activity in the milder degrees of anoxaemia and asphyxia, when produced in unanaesthetized animals.

Given this convenient method of detecting acceleration of the output of adrenalin under these conditions, it was now possible to put to the test the following questions concerning acceleration of adrenalin output and the appearance of hyperglycaemia.

(1) Does asphyxia cause an increase in the output of adrenalin? The production of hyperglycaemia in asphyxia was already well established.

(2) Given that both these effects can be demonstrated as a result of asphyxia, can they be produced by anoxaemia alone?

(3) If anoxaemia can act in this way, does it do so when of the kind and degree encountered in high flying?

It will be seen that all these questions were answered in the positive sense by my experiments. There remained, therefore, for investigation the nature of the mechanism by which anoxaemia caused both these effects, and the further question as to how

far the hyperglycaemia was a result of the accelerated output of adrenalin, and how far it was a more direct result of anoxaemia.

In addition to the experiments which bear directly on the central problem above stated, some incidental observations were made on other more general physiological changes in animals exposed to degrees of anoxaemia, comparable in duration and severity with those to which airmen are subjected.

In flying the ascent and descent are rapid, and the duration of the anoxaemia so produced does not extend beyond an hour or two. The adaptation of man to lack of oxygen in mountain climbing has been described by Haldane (1917), Barcroft (1914), and other workers. It occurs somewhat slowly and is not fully developed for several days. It is unlikely, therefore, that any of the various accommodating mechanisms discussed by them come seriously into operation during high flights, with the possible exception of increase in the corpuscular content of the blood, as indicated by the work of Dreyer and Walker (1913), which the recent work of Bazett and Corbett (1918) seems to confirm. This change, when it appears rapidly during a short period of anoxaemia, must presumably be attributed to loss of plasma from the vessels.

Recently a great deal of attention has been paid to changes in the capacity of the plasma for combining with carbon-dioxide in shock, gas gangrene, and other conditions. It seemed likely that the production of fixed acids in anoxaemia (Araki (1891, 1894)) would cause a fall in the alkali reserve. I have investigated the changes in the alkali reserve in anoxaemia in order to discover if they were of such magnitude as to play any serious part in producing the recognizable symptoms accompanying want of oxygen. Some observations have also been made on the volume of the blood in anoxaemia, with a view to ascertaining whether any alteration, by loss of plasma or otherwise, occurs in the volume of blood in effective circulation.

2. Methods.

Atmospheres containing reduced proportions of oxygen were prepared by the method described by Dreyer (1918), in which air and nitrogen pass through separate meters at accurately adjustable rates, into a mixing chamber from which the mixture is delivered to the subject of experiment.

As a mixing chamber I used for small animals a glass bell-jar holding 22 litres, fixed on a board through which the inlet and outlet pipes passed, the junction of the bell-jar and the board being made air-tight with 'plasticine'. For larger animals the bell-jar was replaced by a glazed stone-ware jar holding 36 litres. When anoxaemia uncomplicated by anaesthesia was to be produced, the mixture of air and nitrogen was administered to the animal by means of a mask. This was formed from a truncated cone of tinplate, oval in cross section. The inlet and outlet tubes were of half-inch bore and were soldered into the closed and smaller end of the mask. A piece of thin sheet rubber was cut into a suitable strip and

joined by rubber solution so as to form a short, wide, conical tube. The broader end of this tube was of considerably smaller diameter than the open end of the mask and was stretched over this latter and bound down round the margin with insulating tape. The narrow end of the tube was then invaginated into the mask and furnished an opening in an elastic diaphragm, which fitted the snout of the animal. Experience in the use of this mask showed that if the rubber was renewed as often as it showed signs of losing elasticity the contact made with the animal's face was practically air-tight, so that it breathed nothing but the mixture supplied to the mask during the time that the latter was in position. The outlet tube of the mask was fitted with an expiratory valve and the inlet tube was connected by wide-bore tubing with the mixing chamber of the Dreyer apparatus. The mask was used successfully with cats, dogs, and goats.

In certain experiments cats and rabbits were placed inside the bell-jar while the mixture of air and nitrogen was passed through it. Analysis of the air from the outlet tube of the bell-jar showed no appreciable increase in carbon dioxide, so that the flow of the mixture was sufficiently rapid to wash out the animal's expired air.

In some experiments the animal was anaesthetized while still in the bell-jar. For this purpose a three-necked Wolff's bottle, containing strips of gauze, was inserted in the path of the flow from the meters to the bell-jar. The middle neck of the bottle was fitted with a dropping funnel from which chloroform or ether could be dropped on to the gauze without opening the apparatus.

When anoxaemia was produced in animals under anaesthesia the mixture of air and nitrogen was supplied to the animal through a tracheal cannula provided with inlet and outlet valves. When a volatile anaesthetic was being administered the mixture was passed through the anaesthetic bottle of the operating table supplied by Palmer. This enabled the amount of anaesthetic administered to be regulated by means of a four-way tap, so that any required fraction of the gas mixture supplied to the animal passed through the anaesthetic bottle. Artificial respiration could be carried out if necessary with this gas mixture by putting the Brodie pump into circuit. Some experiments were made under urethane, in which case the mixture of air and nitrogen was led straight to the tracheal cannula.

The nitrogen used was of 98 per cent. purity and contained a small proportion of oxygen. The calculation of the percentages of oxygen in the mixtures from the meter readings could not, therefore, in any case give a high order of accuracy, but analyses of samples with Haldane's gas-analysis apparatus showed that the correspondence was sufficiently close for my purpose. Table I shows the kind of accuracy obtained. In later experiments the composition was calculated from meter readings only.

No. of Expt.	*TA in seconds.*	*TN in seconds.*	*Calculated* O_2 *%.*	*Observed* O_2 *%.*
1	59	60	10·57	10·52
2	56	201	16·39	16·44
3	29	28·4	10·4	10·6
4	28	17·5	8·0	7·8
5	34·5	31·5	10·0	9·9
6	39	19·5	6·99	6·80

When mixtures were administered to animals over long periods the small variations in speed of the motor which drove the gas compressor caused corresponding small alterations in the rate of flow of air. Frequent readings of the times of flow through both meters were taken and, in addition, the initial and final readings of both meters enabled an average value for the oxygen content of the mixture to be calculated.

Mixtures containing excess of carbon dioxide were obtained by the use of the same apparatus with the substitution of a container filled with this gas for the nitrogen cylinder.

Asphyxia was produced by making the animal breathe into the mask above described, which was connected by one outlet with a long piece of rubber tubing, the other being suitably closed. In other experiments the long tube was replaced by a collapsible air-tight bag connected with the mask by a short, wide tube. Samples of air for analysis could be obtained from this at the end of the period of asphyxia.

Blood samples were obtained in animals under anaesthesia from the cut end of a carotid artery. The animal was bled to the required amount into a centrifuge tube containing a few milligrams of dry powdered potassium oxalate.

In unanaesthetized animals the method used varied with the animal under experiment. In goats and cats samples were removed by a syringe, the needle of which was pushed into one or other of the external jugular veins. Rabbits were bled from the marginal vein of the ear, which was shaved at the margin and warmed to expedite the flow of blood.

The method of determining the blood sugar was a modification of the Lewis-Benedict method described by S. R. Benedict (1918). 2 c.c. of blood, which is prevented from clotting by the addition of solid dry potassium oxalate, are measured in a pipette, which is twice washed out with distilled water—the washings being added to the blood. The volume is made up to 25 c.c. with picric-picrate solution. The mixture is filtered and 8 c.c. of the filtrate are taken. To this 1 c.c. of 20 per cent. sodium carbonate solution is added. This is then placed in a water bath at 100° C. for ten minutes, removed and cooled under the tap and diluted according to strength to an appropriate dilution—12·5 c.c. or 25 c.c. for normal bloods. The mixture is then estimated against a picramic acid standard in the Du Boscq colorimeter—standard being set at 15 mm. The basic standard recommended by Benedict is a solution of 0·64 mg. of glucose dissolved in 4 c.c. of water to which 4 c.c. of picric-picrate glucose solution and 1 c.c. of sodium carbonate (20 per cent. solution) are added—heated for ten minutes in boiling water, cooled and diluted to 12·5 c.c. A solution of picramic acid made up as follows matches this basic standard with the colorimeter set at 15 mm. A stock solution of picramic acid (m.p. 198° C.) containing 100 mg. picramic acid and 200 mg. sodium carbonate per litre is first made. 146 c.c. of this stock solution is taken to which 1 c.c. of 20 per cent. sodium carbonate solution and 15 c.c. picric-picrate solution are added, and the whole made up to 300 c.c. with distilled water. It will be noted that I have found it necessary to modify slightly the standard recommended by Benedict.

An investigation was first carried out by comparing varying strengths of glucose dissolved in 4 c.c. of water to which 4 c.c. of picric-picrate solution and 1 c.c. of 20 per cent. sodium carbonate solution were added, heated at 100° C. for ten minutes, cooled and diluted as follows :

0·64 mg. of glucose treated in this way and diluted finally to 12·5 c.c. matches the picramic standard at 15 mm.

1·28	mg. of glucose—final dilution			12·5	c.c. matches at	7 mm.
1·28	,,	,,	,,	25	,,	14·8 ,,
1·92	,,	,,	,,	18·5	,,	7 ,,
1·92	,,	,,	,,	25	,,	9·3 ,,
1·92	,,	,,	,,	37·5	,,	15 ,,
2·56	,,	,,	,,	25	,,	7 ,,
2·56	,,	,,	,,	50	,,	15 ,,

These results indicate that the amount of reduction of the picric-picrate solution is strictly proportional to the amounts of glucose added, but that the picramic acid so produced undergoes some change on dilution. When the picramic acid is present in too concentrated a form, the readings are too low and sugar percentages calculated from them would be too high. This effect may be corrected by taking a rough reading, diluting to an appropriate degree and then taking a series of exact readings.

The method was then further tested by adding known amounts of glucose to blood of which the natural sugar percentage had been determined. Two series were put up, the blood used being taken from the ear vein of an unanaesthetized rabbit.

Series I.	*Observed B.S. %*	*Calculated B.S. %*
Blood 2 c.c. Final dilution 25 c.c.	0·187	—
Blood 2 c.c.+2·2 mg. glucose. Final dilution 37·5 c.c. Reading 14·7 m.	0·306	0·297
Blood 2 c.c., 4·4 mg. glucose. Final dilution 50 c.c. Reading 15 mm.	0·400	0·407

	Corresponding % as if 2 c.c. Blood were present. *Observed.*	*Calculated.*
2·2 mg. glucose in 4 c.c. of water treated exactly as the blood samples above. Final dilution 25 c.c.	0·225	0·220

Series II.	*Observed B.S. %*	*Calculated B.S. %*
2 c.c. blood. Reading 17·5	0·171	—
2 c.c. blood+0·275 mg. glucose Reading 16·8.	0·179	0·184
2 c.c. blood+0·55 mg. glucose. Reading 15·0.	0·200	0·198
2 c.c. blood+0·825 mg. glucose Reading 14·5.	0·207	0·212

In making observations on the blood sugar of small animals, e. g. cats and rabbits, two complicating factors had to be considered—haemorrhage due to the taking of samples and emotional disturbance in non-anaesthetized animals. It was not possible to eliminate the second factor, and consequently the blood-sugar determinations recorded are frequently too high, *vide* Scott (1914). This, however, does not invalidate my conclusions as it is true of all the observations

on normal cats and rabbits. The haemorrhage effect of taking three or four small bleedings of 2–3 c.c. each was found in control experiments to cause no appreciable rise in the blood sugar, though more considerable haemorrhages, as Epstein and Bahr (1914) have shown, cause a marked hyperglycaemia.

It will be convenient to deal first with the observations on the general effects of anoxaemia before proceeding to those concerned with the more specific subject of inquiry in this investigation.

3. General Effects of Anoxaemia.

It became evident early in the research that most of the experimental work would have to be done under conditions uncomplicated by anaesthesia. Hill and Flack (1908) investigated the respiratory response of the dog and cat under light anaesthesia to atmospheres poor in oxygen but containing excess of CO_2. They obtained graphic records of the respiration of animals under experiment. Though it was not possible to obtain such records in non-anaesthetized animals, caused to breathe atmospheres containing diminished quantities of oxygen by placing them under the bell-jar of the Dreyer apparatus, an opportunity was afforded for observation of the respiration and other effects of anoxaemia of varying degree and duration. These observations were made in greatest detail upon the cat.

The respiration rate of a cat, under normal conditions, was somewhat irregular in rhythm, the rate varying between 25 and 30 per minute. The inhalation of an atmosphere containing 10·4 per cent. of oxygen caused an almost immediate increase in the rate of breathing to 37 and after ten minutes to 44 per minute. The depth of the respiration likewise increased. The animal breathed with its mouth open and tongue protruding. After about fifty minutes the respirations were 30 per minute and much more efficient, so that the animal appeared to be more comfortable. After eighty minutes' inhalation of this atmosphere the percentage of oxygen present was reduced to 8 per cent. The cat responded at once by becoming restless and excited. It exhibited an unusual degree of dyspnoea, for during the first ten minutes after this change of atmosphere the respirations increased to the extraordinary rate of 240 per minute, but were very shallow. The mouth remained open and the animal salivated freely. After twenty minutes the breathing was much deeper, the frequency was 64 per minute and the animal appeared to be much more comfortable. It was now removed from the bell-jar. The heart-beat was forcible and regular and the respiration rate quickly subsided to normal. The cyanosis of the mucous membranes, which had been marked throughout the period of anoxaemia, did not completely disappear for some minutes.

Another cat of 2,400 grm. weight was placed under the bell-jar of the Dreyer apparatus and there subjected for one and three-quarter hours to an atmosphere containing 10·4 per cent. of oxygen. In this case the respiratory response was not nearly so marked as in the previously recorded experiment. The normal rate of respiration was 24 per minute, and when the inhalation of the mixture poor

in oxygen was started this rose to 33 per minute. There was, however, marked increase in the depth of respiration, and though after a quarter of an hour the rate had fallen to 20 per minute, the depth had continued to increase. During this first period of anoxaemia the cat was comfortable and slept part of the time. The percentage of oxygen was now reduced to 9·2 per cent. This corresponds to that obtained at about 22,000 ft., and was maintained for one and a quarter hours. At the beginning of this period the cat exhibited some dyspnoea, but towards its end the respiration was about normal in rate, though excessive in depth. The animal salivated freely and vomited during this time.

After three hours' exposure to an atmosphere poor in oxygen, anaesthesia was commenced with ether by the method described above, the animal remaining in the bell-jar and the percentage of oxygen in the air being increased to 10·6 per cent. When the cat was thoroughly anaesthetized it was removed from the bell-jar and rapidly tracheotomized, and the administration of anaesthetic, together with the mixture of air and nitrogen, was continued. The blood-pressure was recorded and was found to be 160 mm. Hg, a height which was steadily maintained for considerably over an hour. The output of the heart remained good and the heart-beats were regular during this period.

It was evident that prolonged anoxaemia of this degree did not produce any notable change in the efficiency of the circulation.

In cats breathing mixtures containing 7 per cent. of oxygen a characteristic rapid shallow type of breathing with occasional deep sighing inspirations was frequently observed. It is probable that this phenomenon, like the rapid shallow breathing observed in men after gas poisoning by Haldane, Meakins, and Priestley (1918), is explained by a derangement of the normal relation existing between the Hering-Breuer reflex and the regulation of the breathing by chemical stimuli. The administration of atmospheres, containing 7 per cent. of oxygen and over, never caused, in my experience, any loss of consciousness, nor was the animal's sight or hearing evidently affected.

In cats with unpigmented feet, to which mixtures of air and nitrogen were administered by means of a mask, the appearance of the pads afforded useful evidence of the degree of anoxaemia produced. When this was severe the pads became cyanosed and sweated freely.

The respiratory changes observed in the goat were less, and in the rabbit more marked for corresponding degrees of anoxaemia than those observed in the cat.

Despite the fact that determinations of the percentage of oxygen saturation of the arterial blood afford the only absolute index of the degree of anoxaemia produced in an animal, I have not complicated the interpretation of the results of experiments on small animals by taking additional blood samples for this purpose. Observations of the condition of the pads and mucous membranes have been used as evidence of the fact that anoxaemia was being produced. A few observations have been made on the percentage oxygen saturation of the venous blood in the goat, in which animal blood

samples of considerable size could be removed without affecting the haemoglobin value. The observations were made by the method described by van Slyke (1918). The normal content of oxygen in saturated blood for a goat of 15 kilos was 11 volumes per cent. The venous blood normally contained 7·4 volumes, and after inhalation for fifty-five minutes of a mixture containing 8·5 per cent. of oxygen, 3·8 volumes per cent. The percentage oxygen saturation of the venous blood had fallen from 67·3 per cent. to 34·5 per cent. On another occasion the percentage oxygen saturation of the venous blood of the same animal was 62 per cent. before exposure for an hour and a half to an atmosphere containing 9 per cent. of oxygen, and fell to 31·4 per cent. at the end of this period.

4. Effects on the Alkali Reserve of the Plasma and on the Volume of the Blood in Effective Circulation.

Reference has already been made to the recent work on the alkali reserve in shock, gas gangrene, and allied conditions. Observations have been made on the cat and goat in which severe anoxaemia was produced. A few experiments sufficed to show that the diminution of the capacity of the plasma for combining with carbon dioxide was a small and generally evanescent effect, which could not be regarded as playing any serious part in the production of the symptoms following anoxaemia of the degree here in question. The estimations were carried out by the method of van Slyke (1917) on blood obtained from the jugular vein of the animal. To avoid loss of CO_2 before separation of the corpuscles, the blood was transferred, as indicated by van Slyke, directly to centrifuge tubes containing a little dry powdered oxalate covered by a layer of liquid paraffin, and immediately centrifuged.

The experiments were uncomplicated by anaesthesia, and in the cat the effect of haemorrhage (*vide* Milroy (1917)) on the values obtained was eliminated by a suitable control.

A goat weighing 15 kilos inhaled by means of a mask an atmosphere containing 11·4 per cent. O_2 for twenty-five minutes and for the ensuing fifty-five minutes one of 8·5 per cent. The blood samples were of 12 c.c. each. There was no change in the haemoglobin percentage, which was 58 per cent. throughout. The degree of anoxaemia produced is shown by the percentage oxygen saturation of the venous blood which fell from 67·3 per cent. to 34·5 per cent. Before anoxaemia the alkali reserve was 63·9 per cent., immediately after it was 62·0 per cent. and one hour later it was 57·8 per cent.

A cat of 2,300 grm. which, while in the bell-jar, inhaled for one hour and forty minutes an atmosphere containing 7 per cent. of oxygen gave the following results :

Time.	*Hb. %.*	*% CO_2 combining capacity.*
10.20 a.m.	76	34·9
10.40–12.30, cat under the bell-jar.		
12.25 p.m.	72	33·6
2.30 p.m.	62	29·0
3·30 p.m.	74	34·0

Another cat of 3,500 grm. was bled at the following time intervals

without being made anoxaemic. Four samples each of 6 c.c. were taken :

Time.	Hb. %	% CO_2 combining capacity.
12·15 p.m.	100	48·6
12·30 p.m.	100	46·8
1·0 p.m.	97	47·8
2·5 p.m.	92	46·0

A week later its weight was 3,600 grm. ; three samples of 6 c.c. were taken and between the first and second bleedings the cat was placed in the bell-jar of the Dreyer apparatus and breathed an atmosphere containing 7·6 per cent. of oxygen.

Time.	Hb. %	% CO_2 combining capacity.
11·5 a.m.	90	45·8
11.23–11.58 a.m. anoxaemia 7·6 % oxygen.		
12·5 p.m.	90	40·0
1·5 p.m.	87·3	44·9

It is evident from these results that the reduction of the alkali reserve of the plasma due to diminished tension of oxygen in the air breathed and in the circulating arterial blood is not comparable to the severe reduction which occurs when the peripheral circulation through the capillaries is defective even though the arterial blood is saturated with oxygen (*vide* M. R. C. report, 1918). The values obtained for the haemoglobin percentage in these and other experiments did not afford any evidence of loss of volume of the circulating blood. A few direct observations were made on this point using the vital red method introduced by Keith, Rowntree, and Geraghty (1915).

In control experiments on the cat and rabbit, successive determination of the volume of the circulating plasma could be made at one or two hours' interval, with fairly concordant results. When these animals were rendered anoxaemic during the interval between the observations the volume of the plasma was not found to undergo any diminution but rather a slight increase, as the following tabulated observations show :

Animal under experiment.	*Degree of anoxaemia.*	*Initial plasma volume.*	*% corpuscular volume by haematocrit.*	*Initial blood volume.*	*Final plasma volume.*	*% corpuscular volume by haematocrit.*	*Final blood volume.*
Rabbit, 1,850 grm.	Control	60 c.c.	35	92 c.c.	65 c.c. (4 hrs. later)	32·5	96 c.c.
Rabbit, 2,600 grm.	Control	122 c.c.	30·8	177 c.c.	116 c.c. (40 min. later)	32·8	173 c.c.
Rabbit, 2,600 grm.	7 % O_2, 1 hr.	100 c.c.	30·9	145 c.c.	107 c.c.	32·6	158 c.c.
Rabbit, 3,000 grm	7 % O_2, 1 hr.	108 c.c.	29·3	150 c.c.	110 c.c.	24·9	146 c.c.
Cat, 2,500 grm.	9·5 % O_2 1 hr. 35 min.	100 c.c.	35·2	154 c.c.	109 c.c.	35	168 c.c.

In these animals it appears that any small changes in the volume of the circulating blood which may occur as a result of anoxaemia are not detectable with any certainty by this method. There is not, however, any evidence of diminution in volume of the plasma but rather the contrary.

The injection of vital red into a goat of 15 kilos weight was followed by toxic symptoms, and whereas, in the same animal, anoxaemia uncomplicated by such an injection caused no change in the haemoglobin value (*vide supra*), the inhalation of 9 per cent. oxygen for one and a half hours produced on this occasion an increase in the corpuscular content of the blood accompanied by a corresponding increase in the haemoglobin value, as determined both colorimetrically and by calculation from the oxygen-carrying capacity of the blood.

The estimation of the volume of the plasma showed, not a fall in correspondence with this rise in corpuscular content, but an apparent large increase. It is evident, therefore, that in this animal the vital red injected does not remain in the circulating plasma for any appreciable time, and that the results obtained for the volume of the plasma are not to be relied upon.

In one experiment on a dog, although no toxic symptoms were noted, the results obtained for the volume of the plasma showed a large increase as a result of inhalation of an atmosphere containing 8 per cent. oxygen for one hour. At the same time the corpuscular content of the blood was diminished, as shown by a fall in the haemoglobin percentage and directly by haematocrit, though not sufficiently to be in accord with the plasma volume determinations.

It is to be noted that any influence which makes the vital red leave the circulation at more than the normally very slow rate will increase the apparent volume of the plasma. The apparent increase shown in some cases, without a corresponding fall in the proportion of corpuscles, is probably fallacious.

5. The Effect of Anoxaemia on the Output of Adrenalin and on the Blood Sugar.

A. *The Paradoxical Pupil Reaction.*

In cats in which one pupil has been partially denervated by the removal some days before of the corresponding superior cervical ganglion, this sensitized pupil is normally, under conditions of bright illumination, slightly smaller than its fellow. The nictitating membrane is partially prolapsed and the palpebral fissure narrowed on the denervated side.

When the animal is asphyxiated by one of the methods described above, the following changes constantly occur. As soon as the mask is removed both pupils are found to be widely dilated. Half a minute later, the pupils being illuminated meanwhile, either by daylight or by means of an electric filament lamp, symmetrically placed at a fixed distance from the animal's eyes, the normal pupil is contracted down to a slit while the denervated one remains dilated for a variable period. At the end of the asphyxia the nictitating membrane on the denervated side is retracted and the palpebral

fissure wider than that on the normal side. As the denervated pupil contracts the nictitating membrane prolapses and the palpebral fissure becomes narrower.

This reaction is known as the paradoxical pupil reaction. It was first described by Budge (1855). Anderson (1903) gave an historical account of the investigations concerning it which had been carried out up to that time. He obtained the reaction in excitement, asphyxia, and in anaesthesia, and observed that it could be elicited twenty-four hours after the removal of the ganglion and for more than a year afterwards. Meltzer and Auer (1904) showed that it occurred as a result of the injection of adrenalin.

Dale and Laidlaw (1912) used the reaction in investigating the action of certain alkaloids on the adrenal glands. Elliott (1912) arrived at the conclusion that the secretion of adrenalin ' is the cause of nearly all the phenomena of paradoxical pupillodilatation '. He observed that when one superior cervical ganglion was removed in the adult cat, and when subsequently the suprarenals were removed, the dilatation of the corresponding pupil, which before the second operation had followed emotional excitement or light asphyxia, was no longer present, though deep asphyxia still gave dilatation of the denervated pupil in the terminal spasms. Stewart and Rogoff (1916 b), however, observed that in cats in which one suprarenal had been removed and the splanchnics of the opposite side divided, fright, asphyxia, and anaesthesia with ether gave reactions of the denervated pupil ' which did not differ from those reactions in cats whose suprarenals had not been interfered with '. The same workers (1916 a), using their ' pocket ' method in cats under urethane anaesthesia, observed the effects produced by asphyxia on the output of adrenalin as measured by the effect of suprarenal vein blood on the blood-pressure and on the denervated pupil. Their results in these experiments may be interpreted as indicating a slight increase in the output of adrenalin in this condition. They pointed out, however, that the effect of asphyxia in producing rise of blood-pressure and dilatation of both pupils, apart from the effect due to the suprarenals, made it difficult to use these reactions as a measure of the output of adrenalin, and that such positive results as they obtained were capable of interpretation as resulting from increased rate of filling of the caval ' pocket ' with adrenal blood, due to the rise in blood-pressure caused by asphyxia. They also referred to the possibility that the extensive operative procedures adopted in these experiments might, by diminishing the secretion of adrenalin, vitiate any negative conclusions arrived at in this way. In Stewart's experiments the use of the reaction of the denervated pupil as an index of increased output of adrenalin in asphyxia has yielded results difficult of interpretation, because no attempt was made to graduate the severity of the asphyxia used.

Reviewing the evidence I concluded that it was safe to proceed on the assumption that, in the unanaesthetized animal, the paradoxical dilatation was an index of accelerated output of adrenalin in anoxaemia and asphyxia, except in the case of the residual effects, which extreme asphyxia produces even after both suprarenal glands have been removed. The correctness of this assumption received cumula-

tive confirmation as the work proceeded and the points of evidence can most conveniently be noted in connexion with the experiments in which they arose.

Special attention was paid to the extent of the reaction. This may be gauged by (1) the size and shape of the dilated sensitized pupil relative to its fellow of the opposite side and (2) the time taken by the sensitized pupil to attain equality to its fellow. Half a minute after this equality has been attained the denervated pupil was invariably found to have become once more smaller than the normal one. If the effect produced is a maximal one the denervated pupil is circular in outline and only the narrowest margin of iris is visible at its circumference. In less marked reactions angulation is evident in the outline of the pupil at each extremity of its vertical diameter. The time during which the preferential dilatation persists, that is to say the time elapsing between the cessation of the asphyxia and the attainment of equality by the two pupils, varies from ten minutes to less than one minute, according to the severity of the asphyxia and the sensitiveness of the reaction in the particular cat under experiment.

B. *The Part played by Want of Oxygen and by Excess of CO_2 in producing Acceleration of the Output of Adrenalin and Hyperglycaemia in Asphyxia.*

The following experiments upon cats in which the right superior cervical ganglion had been previously removed[1] were made to decide the question of accelerated output of adrenalin. The full experimental details of these and other experiments will be given in another paper.

Cat 1.

1. 11. 18. Removal of the right superior cervical ganglion under ether anaesthesia with aseptic precautions.[1]

2. 12. 18. Cat tied out on the table. No anaesthetic administered. The effects on the pupils of asphyxia, anoxaemia, and excess of CO_2 respectively were observed. Mixtures containing known percentages of CO_2 and of oxygen were passed through a mask which was applied to the animal's face.

a.m.

11.32–11.37. Animal inhaling atmospheric air circulating through the mask.

11.37. No preferential dilatation observed.

11.53–11.58. Animal inhaling a mixture of air and nitrogen containing 7 per cent. O_2.

11.58. Maximal preferential dilatation of the sensitized pupil which persisted for seven minutes.

p.m.

2.38–2.54. Animal inhaling atmospheric air containing 7·4 per cent. of CO_2.

[1] All the operative procedures after which the animal was allowed to recover were kindly performed for me by Dr. H. H. Dale, F.R.S.

p.m.	
2.54.	No preferential reaction observed.
3.17–3.21.	Asphyxia. Mask in position and 6 ft. 9 in. of rubber tubing attached to it.
3.21.	Maximal preferential pupillary reaction which lasted seven minutes.
3.35–3.40.	Animal inhaling atmosphere containing 6·6 per cent. CO_2.
3.40.	No preferential reaction.
3.40–3.47.	Animal inhaling the same mixture.
3.47.	No preferential reaction.

Cat 2. In this animal the effects of the inhalation of atmospheres containing excess of CO_2 and diminished amount of oxygen were contrasted. The right superior cervical ganglion had been removed a month before. The animal was under urethane anaesthesia, and the mixtures were administered by means of a tracheal cannula with inlet and outlet valves.

The inhalation of an atmosphere containing 6·7 per cent. of CO_2 and 19·4 per cent. of oxygen caused no preferential dilatation of the sensitized pupil. The inhalation of an atmosphere containing only 6·8 per cent. of oxygen for four minutes, on the other hand, caused dilatation of both pupils, the sensitized pupil dilating more than its fellow. When air was once again flowing through the cannula the sensitized pupil went on dilating while the normal one contracted till the preferential reaction was almost maximal half a minute after the flow of pure air had commenced. The reaction persisted for seven minutes.

Cat 5. In this animal the right superior cervical ganglion had been removed aseptically under ether eight days before. The following experiments were conducted without anaesthesia. Asphyxia, produced by making the cat breathe into the mask connected with a tube 7 ft. long for four minutes, caused a maximal preferential dilatation of the sensitized pupil which lasted for five minutes. Circulation of atmospheric air through the mask as a general rule caused no reaction, though once a very small and evanescent preferential dilatation of the sensitized pupil was observed. This effect was probably due to emotional causes, as the cat was angry and excited at the time. The animal also inhaled mixtures containing 10 per cent. and 16·5 per cent. of CO_2 respectively. In the first case no reaction was observed, and in the latter the barely perceptible preferential dilatation which was observed may have been due to emotional causes, as the cat struggled a good deal and was very excited. The animal also inhaled mixtures containing 13, 11, 10, 7·5, and 6 per cent. of oxygen respectively with resulting paradoxical pupil reactions which were greater as the anoxaemia became more severe. The inhalation of an atmosphere containing 6 per cent. of oxygen for five minutes, and of pure nitrogen for one minute, both resulted in maximal preferential dilatation of the sensitized pupil which persisted for five minutes.

These and a number of similar experiments made at this time seemed to indicate that the paradoxical pupillary reaction which

occurs in asphyxia is due entirely to the diminution of oxygen and not to excess of CO_2 in the air breathed, and that its duration and extent depends very largely upon the degree of anoxaemia produced. More recent observations have shown that the inhalation of mixtures containing percentages of CO_2 of the order of 15 per cent. regularly cause small paradoxical reactions.

The following experiments upon goats and cats were made to investigate the hyperglycaemia of asphyxia.

A goat weighing 15 kilos whose initial blood sugar was 0·101 per cent. was asphyxiated for three minutes by breathing into a mask to which a bag was attached. A sample of the air from the bag at the end of three minutes contained 7·8 per cent. of CO_2 and 12·3 per cent. of oxygen. The blood sugar rose to 0·136 per cent. On another occasion the administration of an atmosphere containing 3·5 per cent. of CO_2 for half an hour caused a slight fall in the blood sugar from 0·100 per cent. to 0·097 per cent. The inhalation of a mixture containing 7·3 per cent. of CO_2 caused a further fall to 0·091 per cent.

A cat weighing 2,300 grm. whose initial blood sugar was 0·130 per cent. inhaled from a mask a mixture containing 7 per cent. of CO_2. After twelve minutes its blood sugar was 0·120 per cent. and half an hour later it was 0·125. On the same day some hours afterwards, seven minutes' asphyxia produced by re-breathing through a long tube attached to the mask caused a rise of blood sugar from 0·120 to 0·306 per cent.

Some later observations upon cats on the effect of excess of CO_2 yielded results which were difficult of interpretation, because of the large rise of blood sugar which occurred from emotional causes. One such animal which gave initial sugar values of 0·128 and 0·130 per cent., when samples were taken immediately after tying out upon the table, gave an initial blood sugar of 0·193 per cent. when tied out for seven minutes before taking the sample. When tied out for a similar period, during five minutes of which an atmosphere containing 15 per cent. CO_2 and 17 per cent. oxygen was inhaled, the blood sugar rose from 0·130 to 0·222 per cent. Now during a similar period of inhalation of the same mixture there was a fall in the oxygen content of the venous blood, which in itself was sufficient to account for the excess of rise over and above that which occurred as a result of emotional excitement.

In another cat, whose blood sugar was not so sensitive an index emotional excitement, a small rise of blood sugar was obtained with the inhalation of an atmosphere containing 5 per cent. CO_2, though no rise was noted as a result of the inhalation of air by the mask for the same period. The inhalation of a mixture containing 15 per cent. CO_2, but with the oxygen content reduced to 17 per cent., showed a rise in the blood sugar from 0·119 to 0·197 per cent.

In still another cat, which had had the right superior cervical ganglion excised aseptically under ether some days before, and in which the blood sugar was very sensitive to emotional disturbance, the inhalation of 5 per cent. CO_2 for five minutes gave a rise from 0·206 to 0·240 per cent. in the blood sugar. The inhalation of atmospheric air for the same period gave a rise which was quite comparable with this, i. e. from 0·176 to 0·206 per cent. In neither

case was there any paradoxical dilatation of the pupil. When, however, an atmosphere containing 15 per cent. of CO_2 and 17 per cent. of oxygen was inhaled for the same period, the blood sugar rose from 0·240 to 0·349 per cent. and there was at the same time a small but definite paradoxical reaction lasting for one minute.

The inhalation of a mixture containing 17 per cent. of oxygen without excess of CO_2 gave no pupil reaction, but caused a rise in the blood sugar from 0·154 to 0·209 per cent.

Of the three possible factors, emotional disturbance, anoxaemia, and excess of CO_2, which might be regarded as playing some part in the production of these effects of asphyxia, there can be no doubt about the rôle of the first two. Mathison (1910–11) has demonstrated the effectiveness of high percentages of CO_2 in stimulating the bulbospinal centres, and from the observation recorded above it is evident that percentages of CO_2 of the order of 15 per cent. can cause acceleration of the output of adrenalin and hyperglycaemia. The part played by excess of CO_2 in asphyxia requires further investigation.

For the present purpose it is sufficient to know that anoxaemia can by itself cause both these effects of asphyxia.

C. *Does Anoxaemia of the Degree and Duration met with in Flying at High Altitudes suffice to produce these Effects?*

The evidence submitted later in connexion with the mechanism of production of these effects cannot be adduced in answer to this question, because for this latter purpose it was found convenient to make the experimental animals inhale atmospheres deficient in oxygen to varying extent for very brief periods, e. g. five to six minutes, and the change from normal air to such atmospheres was sudden and not at all comparable to the more gradual diminution of oxygen tension during the ascent to a height. It was not to be expected that such definite pupil reactions would be obtained with gradual as with sudden development of anoxaemia.

Some experiments with *Cat 5*, before its splanchnic nerves were divided, in which the animal was rendered anoxaemic by being placed under the bell-jar of the Dreyer apparatus, pointed to this conclusion. Inhalation of 13·3 per cent. oxygen for five minutes by means of the mask gave in this cat a definite preferential pupil reaction. When the animal inhaled 9 per cent. oxygen under the bell-jar and some three or four minutes were taken in reducing the oxygen content of the air breathed to this level, though the nictitating membrane was retracted no definite pupil reaction was obtained. When the oxygen present in the mixture was further reduced to 7 per cent. a definite pupil reaction was obtained after five minutes.

This sort of result suggested that the emotional disturbance produced by tying the animal out on the table and administering mixtures deficient in oxygen by means of a mask had a distinctly adjuvant effect on the acceleration of the output of adrenalin by anoxaemia.

No difficulty was experienced in showing that anoxaemia of the degree associated with high flying is sufficient to cause hyperglycaemia, though brief, suddenly produced anoxaemia is much more potent in causing rise of blood sugar than prolonged anoxaemia with more

gradual onset. A partial explanation is to be found in this case in the fact that time is allowed for the excretion of sugar in the urine.

There is nothing new in the production of glycosuria by anoxaemia. Araki (1891) produced glycosuria in animals rendered anoxaemic to unknown degrees, and showed that at the end of such experiments their blood contained excess of sugar.

I have made experiments on rabbits, cats, and goats, which for this purpose were not anaesthetized. A rabbit weighing 2,300 grm. with an initial blood sugar of 0·189 per cent. was placed under the bell-jar of the Dreyer apparatus. The bell-jar was ventilated with atmospheric air for half an hour and at the end of this time the blood sugar had risen to 0·197 per cent. The inhalation of an atmosphere containing 8 per cent. of oxygen for an hour caused a rise in the blood sugar to 0·272 per cent. A control animal bled at corresponding time intervals gave successive blood sugar readings of 0·176, 0·176, 0·167, and 0·166 per cent. Successive haemorrhages of 2½ c.c. in this animal did not cause any rise in the blood sugar. The additional emotional disturbance caused in the experimental animal by placing it under the bell-jar caused a small rise from 0·189 to 0·197 per cent.

A cat of 2,800 grm. weight, with a normal blood sugar of 0·131 per cent., was placed under the bell-jar through which atmospheric air was circulating. After thirty-five minutes its blood sugar was found to be unchanged. The percentage of oxygen in the atmosphere breathed by the animal was then lowered to 7·3 per cent. and the cat remained under the bell-jar for over two hours at the end of which time its blood sugar was 0·156 per cent. Forty-five minutes later it had risen still further to 0·175 per cent., and two hours after the period of anoxaemia it was 0·123 per cent.

A goat of 14 kilos with an initial blood sugar of 0·077 per cent. inhaled by means of a mask a mixture containing 11·4 per cent. of oxygen. After twenty-five minutes the percentage of oxygen was further diminished to 5·5 per cent. After the inhalation of this atmosphere for rather less than an hour the blood sugar was 0·098 per cent. and an hour later, during which time the animal breathed normal air, its blood sugar had once more returned to 0·078 per cent.

There can be no doubt from the experimental evidence submitted that anoxaemia of the degree met with in high flying is capable of causing hyperglycaemia, and while the accelerated output of adrenalin under the same circumstances is more difficult to demonstrate its occurrence may reasonably be inferred.

D. *The Nature of the Mechanism by which Anoxaemia causes Accelerated Output of Adrenalin and Increase in the Blood Sugar.*

In order to investigate the manner in which anoxaemia produced these effects, experiments were made upon cats in which the right superior cervical ganglion had been removed some days previously. Two separate kinds of experiment were made. In one, such cats were anaesthetized with volatile anaesthetic and subsequently with urethane. Pure nitrogen was administered for short periods by means of a tracheal cannula provided with inlet and outlet valves

before and after removal of the suprarenal glands, or with and without occlusion of the aorta above the origin of the vessels supplying these organs. Finally, the animals were killed and observations were made on the isolated iris preparations in oxygenated Ringer's solution, by the method devised by Dale and Laidlaw (1912).

In the other type of experiment the blood-sugar change and pupil reactions were studied in cats with sensitized pupils which were not under anaesthesia when the observations were made. Various mixtures of air and nitrogen were administered by means of a mask for short periods (five minutes) and the maximal oxygen content of the mixture necessary to produce (1) rise in blood sugar, and (2) preferential dilatation of the denervated pupil was determined.

(i) In the intact animal.
(ii) In the animal in which all the splanchnic fibres had been divided proximal to the semilunar ganglion some days before, and time allowed for the cat to get back to its normal weight.
(iii) In the animal with the splanchnics divided and the adrenal glands removed. Time was allowed for the effect of the anaesthetic to pass off, but the observations were made before definite symptoms due to removal of the suprarenals had occurred.
(iv) In other cats with the splanchnic fibres intact but with the adrenals removed. Here again the observations were made before the symptoms due to decapsulation had appeared.

In this report I propose to state only the general results of these experiments. The full protocols will be published later.

(a) *Experiments under urethane anaesthesia and observations on the iris preparations in vitro.* In these experiments the administration of a volatile anaesthetic caused a preferential dilatation of the denervated pupil which was not, however, very marked under urethane, but which in some animals made it difficult to say when a paradox due to anoxaemia had passed off.

Before removal of the suprarenal glands the administration of pure nitrogen for one and a half minutes caused dilatation of both pupils. As soon as the inhalation of nitrogen was stopped the normal pupil contracted down rapidly, while the denervated one remained dilated for some minutes. This reaction was often almost maximal. After the suprarenal glands had been removed a similar administration of nitrogen gave quite a different pupil reaction. Though both pupils dilated somewhat while the nitrogen was being inhaled—the normal one now rather more than the sensitized one—as soon as air was once more passing through the cannula they contracted down quickly. The preferential dilatation of the denervated pupil was no longer present in response to this degree of anoxaemia when the suprarenal glands had been removed.

Similar results were obtained by occluding the aorta above the level at which the arterial supply to the suprarenal was given off. Anoxaemia during such occlusion did not give rise to any paradoxical pupil reaction or only to a very trivial effect, but a marked preferential reaction appeared when the vessel was released.

In order to analyse the changes in the pupils which resulted from anoxaemia in the urethanized animal use was made of isolated iris preparations. It was important to know what the direct effect of urethane was upon the normal and upon the denervated iris, and whether the paradox which occurred under urethane anaesthesia was due to the direct action of the drug on the denervated dilator of the iris, or was produced indirectly by stimulating suprarenal activity. The effect of anoxaemia upon the isolated preparations was also of interest because of its bearing upon the ' residual paradox ' which sometimes occurred in severe anoxaemia after the adrenals had been removed. These preparations were made from the excised eyeballs by cutting away the sclerotic just behind the cornea-sclerotic junction. The cornea was likewise cut away and the lens removed. Any tags of lens capsule or suspensory ligament were carefully clipped off with scissors and the iris was left supported by a stout ring of cornea-sclerotic junction tissue. The preparations were placed in a beaker containing 250 c.c. of Ringer's solution at a temperature of 36–37° C. which rested on a white tile in a constant temperature bath.

In such preparations the pupils rapidly contracted down till they were equal slits when oxygen was bubbled through the Ringer. The addition of adrenalin to the oxygenated Ringer so as to make a 1 in 2,500,000 solution caused a well-marked preferential effect in such a pair of isolated irises. The normal iris remained contracted while the denervated one dilated up to about half the size of a maximal dilatation in the living animal. Adrenalin in the strength of 1 in 25,000,000 did not give any result.

When the Ringer was changed the dilatation of the denervated pupil gradually passed off and the pupils were once more equal and contracted. The addition of 1 grain of urethane dissolved in 10 c.c. of saline so as to make a 1 in 260 solution with the fresh oxygen at Ringer also caused a preferential effect, the normal pupil remaining contracted while the denervated one dilated, not, however, to such an extent as it did with adrenalin of the strength mentioned above. When the Ringer was once again changed this inequality of the pupils gradually disappeared.

When nitrogen was bubbled through the Ringer in place of oxygen a gradual and equal dilatation of both pupils occurred. This dilatation was not a very large effect and never exceeded about one-fourth of the full dilatation of the pupil as observed in the living animal. The replacement of the nitrogen by oxygen caused the pupils to contract down to slits once more. There was no trace of any direct preferential action of anoxaemia upon the denervated dilator.

The effect of urethane and of adrenalin was also tested when nitrogen instead of oxygen was bubbled through the Ringer. It was found that the preferential effects still occurred though now the normal pupil was somewhat dilated and the denervated one more so than during the application of a similar dosage to the preparations when the Ringer was oxygenated.

(b) *Experiments on unanaesthetized cats in which the right pupil had been previously sensitized by removal of the corresponding superior cervical ganglion.*

(i) *Results in the cat with intact splanchnics and suprarenals.* It was occasionally found that when the animal was excited and when it struggled a good deal while being tied down for the experiment there was a preferential dilatation of the denervated pupil. A similar result was sometimes obtained when air was inhaled through the mask for five minutes. Such effects were by no means invariable and varied in different cats and even in the same cat at different times. For instance, when several observations were made on a cat in the course of a day, it became more excitable and more easily gave the reaction. These effects however were, when present, small in extent and short in duration compared with the reactions resulting from anoxaemia.

There was some variation in the sensitiveness of different animals to anoxaemia. Generally speaking, percentages of oxygen as high as 13 and 14 per cent. administered for five minutes gave definitely recognizable preferential reactions and the reaction obtained became more marked as the mixtures breathed contained less oxygen. Mixtures containing 5 per cent. oxygen breathed for five minutes usually produced maximal preferential dilatation of the denervated pupil and the effect lasted several minutes.

The increase in the blood sugar was found to be much more easily influenced by excitement. Mere application of the mask ventilated with pure air was found to cause a small rise in the blood sugar and mixtures containing more oxygen than those necessary to give pupil reactions gave a well marked increase in the blood sugar.

It was conceivable that changes in the blood sugar were a more sensitive index of accelerated output of adrenalin than was the paradoxical reaction. It was found that 0·1 c.c. of 1 in 200,000 adrenalin injected into the ear vein gave a well marked rise in the blood sugar without giving any pupillary paradox. It was also possible that excitement and anoxaemia alike stimulated the central nervous system and through sympathetic stimulation caused increased mobilization of sugar by the liver. There was, however, no evidence in the experiments under discussion as to which of these explanations should be invoked to explain the greater sensitiveness of the blood-sugar changes to anoxaemia and to emotional excitement. It did not appear to be possible to differentiate these two effects. That the second suggested explanation is partly responsible is indicated by the behaviour of animals in which the adrenals have been removed leaving the splanchnics intact. At all events in the normal animal the inhalation of mixtures containing, say, 10 per cent. of oxygen, which caused only a moderate pupil reaction, frequently doubled the percentage of sugar in circulation.

(ii) *Results in the cat with the splanchnics divided proximal to the semilunar ganglion but with the adrenals intact.* The splanchnics were divided in these cats through two flank incisions under ether anaesthesia with full aseptic precautions by Dr. H. H. Dale. After some days, during which the only noticeable symptom which followed the operation was diarrhoea, when the cat had regained its normal weight and its operation wounds were soundly healed, observations were made as in the normal animal before division of the splanchnics.

Section of the splanchnics was found to abolish completely the effects of emotional excitement both on the blood sugar and on the output of adrenalin. Further, the ' threshold value ' of anoxaemia required to cause these effects was now more severe than in the intact animal.

In one cat it was found that only atmospheres containing percentages of oxygen sufficiently small to cause a definite pupil reaction now gave rise to increase in the blood sugar. For instance, before and after the inhalation of an atmosphere containing 10 per cent. of oxygen, the blood sugar was 0·108 per cent. and the inhalation caused no paradoxical dilatation of the pupil. An atmosphere containing 9 per cent. oxygen on the other hand, which gave a definite preferential pupil reaction when inhaled for the same time, also caused a rise of the blood sugar from 0·108 to 0·182 per cent. Repeated observations on this cat showed that for the production of both the accelerated output of adrenalin and hyperglycaemia the ' threshold value ' was the same, about 9 per cent. This somewhat unexpected result, in view of the fact that amounts of adrenalin too small to cause a pupil reaction are efficient in producing a rise in the blood sugar, was not an invariable phenomenon after section of the splanchnics. In another cat the ' threshold value ' for the production of hyperglycaemia was, as might be expected, a somewhat less severe grade anoxaemia than that required to produce a pupillary paradox, but a very much more severe degree of anoxaemia was required to produce both these results than in the same animal before the splanchnics were divided.

So definite is the picture presented by the animal with its splanchnics divided that in two cats in which the operation of division of these nerves was attempted it was possible to decide that some of the splanchnics had not been divided at operation. In one case this was confirmed at autopsy and in the other a second operation was successfully carried out for the division of the remaining intact fibres.

(iii) *Results in the cat with the splanchnic nerves divided and the adrenal glands removed.* The adrenals were removed under full ether anaesthesia with aseptic precautions by Dr. H. H. Dale. Great care was taken in these operations to secure absolute haemostasis. The cats usually lapped milk within a couple of hours of the end of the operation, and five hours after this time, when they had completely recovered from the anaesthetic, they were practically indistinguishable from normal animals. They walked about the laboratory of their own volition and sprang down from benches and tables when placed there.

The effect of the removal of the adrenals in animals whose splanchnics had already been divided was to make them still more insensitive to anoxaemia as far as its effect on the output of adrenalin and the blood sugar were concerned. For instance, in the cat referred to in the previous section, in which a certain parallelism had existed after the section of the splanchnics between accelerated output of adrenalin and hyperglycaemia, this parallelism appeared to persist after removal of the suprarenals. Before this latter operation the inhalation of an atmosphere containing 9 per cent. of oxygen produced both these effects, whereas after the removal of the glands the administration

of an atmosphere containing 8 per cent. oxygen caused no change in the blood sugar and did not give rise to any trace of a paradox reaction. When, however, an atmosphere containing 6 per cent. of oxygen was inhaled for five minutes, a very small paradox resulted which lasted for three minutes and this was accompanied by a rise in the blood sugar from 0·109 to 0·155 per cent. On the following day no pupil reaction could be obtained even when the animal inhaled pure nitrogen for one and a half minutes, at the end of which time its respiratory centre gave out temporarily. At the same time there was a small rise in the blood sugar from 0·083 to 0·109 per cent.

The residual paradox obtained with severe anoxaemia in this and other cats will be more fully considered later. The failure to elicit it a second time suggests that it is due to the stimulation by anoxaemia of extra-adrenal chromaffin tissue, which, being small in amount, gives only a weak adrenalin effect and is readily exhausted.

The parallelism between suprarenal activity and hyperglycaemia in this cat may be explained by the insensibility of its liver cells to the direct effect of anoxaemia. In another cat in which the suprarenals had been removed after previous division of the splanchnics, the inhalation of an atmosphere containing 6 per cent. oxygen for seven minutes caused a rise in the blood sugar from 0·139 to 0·333 per cent. without any trace of paradox occurring. In this latter animal there can be no doubt of the susceptibility of its liver cells to the direct effect of want of oxygen.

There still remains for explanation in the first-mentioned cat the departure from the parallelism which it had previously exhibited when, twenty-four hours after the removal of its adrenals, it gave as a result of severe anoxaemia a small rise in the blood sugar without any paradoxical reaction. Possibly adrenalin was produced in insufficient amount to cause a pupil reaction, or more probably this extreme anoxaemia had a direct effect on the liver cells.

(iv) *Results in the cat with the splanchnics intact but in which the adrenals have been removed.* In these cats the operative procedure was the same as that in the cats in which the splanchnics had been previously divided. Care was taken not to injure the splanchnics during the operation, which was performed aseptically under ether by Dr. H. H. Dale. The observations were made when the animal had completely recovered from the anaesthetic, but before the development of symptoms to the absence of the suprarenals. In such animals emotional excitement and anoxaemia of only moderate severity can still cause hyperglycaemia. The result affords a striking contrast to that obtained in cats in which the adrenals were removed after the splanchnics had been divided.

In one cat before the removal of the adrenals the inhalation of an atmosphere containing 10·5 per cent. of oxygen for five minutes caused a rise in the blood sugar from 0·106 to 0·206 per cent. After the removal of the suprarenals the inhalation of the same atmosphere for a similar time caused a rise from 0·150 to 0·203 per cent. Care must be taken in arguing from the less marked rise of blood sugar in this latter case, because the anaesthesia must have lowered the glycogen content of the liver.

In this particular cat the inhalation of an atmosphere containing

5 per cent. oxygen for five minutes gave a small residual paradox which lasted for over five minutes to equality. It was eight minutes before the normal pupil relations were again established. One hour afterwards the inhalation of pure nitrogen for one and a half minutes, at the end of which time the respiration failed, was ineffective in producing even the smallest paradox. Such a weak and prolonged adrenalin effect is very suggestive of the stimulation of extra-adrenal chromaffin tissue by severe anoxaemia, and the fact that the source of adrenalin or adrenalin-like substance is easily exhausted is also in favour of this hypothesis.

It is evident from the blood sugar results, obtained from these cats with intact splanchnics but with the suprarenals removed, that in the intact animal hyperglycaemia due to emotion or to anoxaemia is largely an effect of the stimulation of the central nervous system and the consequent passage of impulses through the splanchnics to the liver as well as to the suprarenals.

(v) *Conclusions drawn from the results of the experiments above described.* It is apparent that anoxaemia produces a rise in the blood sugar and at the same time accelerates the output of adrenalin. In the normal animal the mere excitement incidental to the observations is sufficient to produce both these effects in some degree. It cannot be doubted, therefore, that this excitement is a contributory factor to the larger effects in this direction produced by mild degrees of anoxaemia in the normal animal. In such an animal the whole of the effect produced by these degrees of anoxaemia appears to be due to stimulation of the central nervous system whether by anoxaemia or otherwise. This stimulus gives rise to the passage of nervous impulses along the splanchnics which cause a mobilization of sugar in two ways—directly by action on the liver cells of impulses reaching them through the splanchnic innervation of that organ, and indirectly by accelerating the output of adrenalin, which in turn acts on the liver. It seems, then, that the glycogenic function of the liver is under a twofold control, and in this respect the liver resembles other organs supplied by the sympathetic.

In the more severe anoxaemia which corresponds to the threshold value of stimulus in the cat with the splanchnics divided, a further factor in the effect of such degrees of anoxaemia on the intact animal is isolated. The direct action of want of oxygen of this degree on the suprarenal, apart from any stimulation of the central nervous system, causes increased output of adrenalin with its consequent effect on the blood sugar. When the anoxaemia is still more severe there appears to be a direct action of want of oxygen on the liver cells themselves causing increased mobilization of sugar.

There remains for consideration the residual paradoxical pupil reaction which occurs in some animals in extreme asphyxia or anoxaemia, even when the adrenals are removed.

Several possible explanations suggest themselves.

1. That the removal of the superior cervical ganglion makes the dilator of the iris unduly sensitive to severe degrees of anoxaemia. This suggestion is negatived by the experiments referred to above on the isolated iris preparation.
2. That the accessory chromaffin tissue may conceivably yield

enough adrenalin to the intense stimulus of severe anoxaemia to account for the occurrence of the pupil reaction after removal of the adrenals.

3. That some substance other than adrenalin, which has a similar action on the sensitized pupil, may be produced in the body as a result of intense anoxaemia.

It may be noted that Elliot (1912) sometimes observed a slight dilatation of the sensitized pupil on stimulating the splanchnics in the eviscerated and decapsulated animal. On the other hand, Cannon and Hoskins (1911) found evidence of the output in response to extreme asphyxia of a substance inhibiting the isolated intestine even after decapsulation, and ligature of the aorta and inferior vena cava at the diaphragm and of the carotids in the neck. It is difficult to suppose that sufficient accessory chromaffin tissue remains accessible to the circulation after such a procedure. Dale and Laidlaw (1912) found evidence under somewhat similar conditions of the output of a substance dilating the pupil in response to nicotine.

The only evidence in my experiments which bears upon this question is the fact that, in two animals in which the suprarenals had been removed, a moderately severe anoxaemia elicited this residual phenomenon, while subsequent attempts to produce it failed completely, despite the use of even more severe degrees of anoxaemia.

This suggests that in the causation of the residual paradox some substance is used up or the mechanism that produces it is so fatigued that it is not possible to reproduce the effect. In both of these cats the effect, though small in intensity, was extremely prolonged, and suggested a prolonged though very small output of adrenalin. The behaviour of these two animals seems to me to lend support to the view that the residual paradox is due to the output of adrenalin from accessory chromaffin tissue which is stimulated by extreme degrees of anoxaemia, and that this tissue is readily exhausted. It should be emphasized that this residual effect, whatever its cause, is a relatively trivial and inconstant element in the paradoxical dilatation of the pupil as produced by asphyxia in the normal animal, and that it cannot contribute significantly to the effect of the milder degrees of anoxaemia.

6. The Probable Value of the Blood-Sugar Changes in Anoxaemia as a Test for Flying Officers.

No experiments on the effect of anoxaemia on the sugar content of the blood of man have been made, but the results of the animal experiments described in this report offer presumptive evidence that the hyperglycaemic reaction to anoxaemia may furnish a useful test, both in the investigation of the fitness of individuals as flying officers, and in determining in doubtful cases of 'flying sickness' whether the patient is fit to resume flying.

In devising such a test there are two possible alternative methods, (1) a determination of the 'threshold' degree of anoxaemia, i. e. the percentage of oxygen in the atmosphere inhaled which just sufficed to cause a hyperglycaemia, or (2) a determination of the

degree of hyperglycaemia produced by the administration of an atmosphere deficient in oxygen to a known degree. It is possible that investigation in man might demonstrate that these two methods yielded parallel results, in which case the second, since it would involve less time and fewer blood samples, would be preferable. A mixture of air and nitrogen containing some known percentage of oxygen would be supplied to the person under investigation by means of a suitable mask for five minutes, and blood samples taken with aseptic precautions from one or other median basilic vein before and after this procedure. The investigation of a series of normal persons would be necessary to select the degree of anoxaemia best suited for such a purpose. If objection were taken to the removal of small venous samples, the sugar estimations might be carried out by a ' micro ' method on samples of capillary blood.

While it must be quite clearly understood that the hyperglycaemia which in animals follows the sudden development of anoxaemia of brief duration is not a measure of the output of adrenalin under these circumstances, such a change in the sugar content of the blood has a definite significance. It has been noted that in animals on which a test of this kind has been made emotional excitement produced by the procedure itself, even when no anoxaemia is entailed, frequently suffices to produce a hyperglycaemia. It is reasonable to expect that this factor of ' excitement ' would be more or less eliminated by the intelligent co-operation of the subject in carrying out the test upon normal individuals. The test would in such a case give evidence of the sensitiveness to anoxaemia of the central nervous system of the person tested. For this purpose it is immaterial whether the effect of the anoxaemia is mediated by the passage of a nervous impulse to the liver *via* the splanchnics, or whether it is due to a nervous impulse going to the adrenals by the splanchnics and causing mobilization of sugar by means of the chemical mechanism of the increased output of adrenalin.

There are, however, certain fallacies which it would be necessary to guard against. The reaction of the individual would be dependent not only on the sensitiveness of the central nervous system to stimulation by anoxaemia but on the ' adrenal load ', that is the amount of available adrenalin present in the suprarenal glands, and also on the content of the liver in glycogen. The question of the relation of the test to the taking of food and to the general condition of the person tested would have to be gone into with some care. In nervous individuals it would not be possible to eliminate entirely the added element of nervous excitement. This fact would, however, operate in the right direction in increasing the blood sugar more than normally, and such individuals would not be suitable as flying officers. It is probable also that many patients suffering from various forms of flying sickness could conveniently be classified with regard to their fitness for flying by means of such a test.

There are one or two objections to the introduction of such a test for general use. First, it may be thought that the test is too elaborate, and to this objection it may be said that now that we are no longer at war, and it is necessary to select pilots for general aeronautics, the question of their selection should be based upon ideal considerations

and not upon the exigencies of the moment. A much more serious objection to its use, in the case of officers who are suffering from 'flying sickness', is that a test of this nature may conceivably make the patient more nervous and militate against his improvement. Generally speaking, in these doubtful cases, if the application of the test operated in this way there would be no doubt as to the unfitness of the individual in question for flying. Lastly, it seems important to point out that a great many observations will have to be made on normal persons and also on those who are definitely unfit for flying before any positive pronouncement concerning its value can be made.

I wish to acknowledge my indebtedness to the Medical Research Committee, who kindly allowed me to carry out the experiments here described in their Department of Biochemistry and Pharmacology, also to the Head of that Department, Dr. H. H. Dale, in whose laboratory this work has been done, for much help and advice, in addition to his kindness in performing for me the various necessary operations from which the experimental animals were allowed to recover.

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IX. THE EAR IN RELATION TO CERTAIN DISABILITIES IN FLYING

BY

SYDNEY SCOTT, F.R.C.S.

(Late Temporary Major, R.A.M.C.)

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PRELIMINARY.

ON February 26, 1918, I received a request from the Director General A.M.S. to give up my civil duties and proceed to France 'to investigate certain questions connected with the special disorders of flying'. . . . Accordingly I rejoined the B.E.F. for about four months. While in France I examined upwards of 300 flying officers, more than half of whom were affected by one or more of the following complaints: deafness, discharge from the ear, rhinitis, pharyngitis, tonsillitis, eustachian obstruction, cerumen, tinnitus, vomiting, vertigo.

The other 150 include officers who were examined whilst on duty with their respective Air Force Units in the field. They comprise normal individuals, those who complained of headache after flying, faintness in the air, and others who had been concussed by a crash, &c. They include pilots who were making bad landings without crashing, as well as flight commanders and leaders who possessed exceptional flying and fighting ability: a number of these volunteered to serve as controls in comparing the results of rotation and other special labyrinth tests. Some flying observation officers, who were applying to be trained as pilots, were also tested.

All officers admitted to hospital were systematically examined by the medical officers attached to the Air Force before being sent to me. The majority were seen in co-operation with Lieut.-Colonel James L. Birley, the late Captain (and afterwards Lieut.-Colonel) C. Dudley H. Corbett, Captain H. C. Bazett, M.C., or Captain James Wyatt. When an ophthalmological examination was necessary, it was undertaken by Captain Foster Moore, Captain H. P. Gibb, or Captain Juler, the ophthalmic medical officers in the Administrative Area. The majority of those seen in the field were examined in conjunction with Captain Porteous, medical officer to the 11th Wing.

A routine examination was made of the ears, nose, and throat, including the eustachian tubes. Seventy-five officers were submitted

to special labyrinth tests in the rotation chair. After analysing the data from a series of sixty-two cases the rotation tests were abandoned, because the results were considered to show these tests were unnecessary for the purpose of investigating the special ailments attributable to flying. Incidentally it was inferred that the rotation tests did not serve to discriminate qualities either favourable or unfavourable to individual flying ability. (See Part 2.)

Table A.

A. ft.	*B.* mm. Hg.	*C.* mm. Hg.	*A.* ft.	*B.* mm. Hg.	*C.* mm. Hg.
	370	390	10,000 . .	530	230
20,000 . .	380	380	9,000 . .	550	210
19,000 . .	390	370	8,000 . .	570	190
18,000 . .	400	360	7,000 . .	590	170
17,000 . .	410	350	6,000 . .	610	150
16,000 . .	420	340	5,000 . .	630	130
15,000 . .	430	330	4,000 . .	660	100
14,000 . .	450	310	3,000 . .	680	80
13,000 . .	470	290	2,000 . .	710	50
12,000 . .	490	270	1,000 . .	740	20
11,000 . .	510	250	Sea-level .	760	0°

A. Altitude in feet.
B. General barometric pressure in mm. Hg. (Approximate.)
C. Excess of pressure; compressing the drum when the eustachian tube fails to open during descent from the altitude given in Column *A* to sea-level. (Approximate.)

1. Abnormal Appearance of the Tympanic Membrane resulting from Flying especially after Rapid Descent from High Altitudes due to Imperfect Action of the Eustachian Tubes.

Many airmen, after flying to high altitudes, are liable, under certain conditions, to be temporarily affected to some extent by deafness, discomfort or pain in the ears, headaches, dizziness, nausea, fainting or vomiting, on returning to the denser atmospheric pressure of low altitudes. In these circumstances an inspection of the airman's ear with mirror and speculum *immediately* after landing shows a marked change from the normal; the fundus is bright red, owing to distension of the blood vessels in the tympanic membrane and mucosa of the middle ear. In extreme cases the tympanic membrane is strongly invaginated[1] into the tympanum; the membrane closely embraces the neck and handle of the malleus and the short process of the incus and incudo-stapedial joint, and is evenly moulded over the edge of the fossula rotunda. Occasionally globules of mucus can be observed through the invaginated drumhead within the cavum tympani.

Reference to the accompanying table (Table A) will serve to recall that the atmospheric pressure at, say, 18,000 ft., is approximately 400 millimetres of mercury, as compared with 760 millimetres at sea-level; assuming the eustachian tubes open regularly while ascending but fail to open during the descent from 18,000 ft., there

[1] I suggested the term 'invagination' as representing the extreme displacement of the tympanic membrane, which I met with among high-flying airmen.

would be an excess of gradually increasing pressure on the outer surface of the tympanic membranes, over the pressure within the tympanic cavity which would attain a pressure equal to 360 millimetres of mercury, on returning to sea-level.

Some aviators who had not learned how to prevent discomfort and misery on returning from high patrols have actually given up flying, and others, similarly affected, have contemplated doing so. After being taught the effect of auto-inflation when *starting* to dive, and *repeating the self-inflation frequently during the descent*, many added a new lease to their flying career.

When, for the purpose of this investigation, I was making a descent from between 19,000 and 20,000 ft., I became aware of the increasing atmospheric pressure on my ear drums at about 16,000 ft. The relief from self-inflation at this height lasted down to about 13,000 ft. when self-inflation again removed all trace of discomfort. While descending below 10,000 ft., the increasing pressure on the ear-drums became noticeable more and more quickly, for swallowing did not suffice to open the eustachian tubes rapidly enough to prevent this. By repeating the inflation at every 1,500 ft. descent, and then every 1,000 ft., even the slightest discomfort and traces of deafness disappeared, and after self-inflating again while a few hundred feet up, I was able to land free from any abnormal sensations in the ears.

In an unbroken ascent we meet with auditory symptoms only occasionally. An officer with eustachian obstruction was more comfortable at between 4,000 and 5,000 ft. than near sea-level, but became affected at 11,000 ft.;[1] another with bilateral obstruction complained of ear distress at 11,000 ft. On attaining 11,000 ft. in a flight which had then taken nearly a quarter of an hour, I became suddenly and unexpectedly conscious of a desire to 'clear' my ears: the sensation resembled that experienced during the earlier stages of a descent though swallowing did not give the expected relief. I realized the sensation must be due to the tympanum being relatively too full of air owing to the expansion of the air within the middle ear, which corresponded to the falling atmospheric pressure in the external ear. My eustachian tubes did not open when swallowing to relieve this sensation, but a very carefully graduated self-inflation, just sufficient to open the tubes, caused the feeling of fullness in the ears instantly to cease, nor did it recur during flight, even when climbing nearly 9,000 ft. higher still.

Function of Eustachian Tubes while Flying.

Normally, the eustachian tubes open once only during each act of swallowing: any difference in atmospheric pressure within and without the tympanic cavity is thus equalized. Even when the tubes act normally it is necessary to swallow repeatedly and frequently to keep pace with the continuous and often rapid changes of pressure which take place during descents. When flying at great height for long, and especially if engaged in the exertions of aerial

[1] This case I described in detail in the *Proceedings of the Royal Society of Medicine*, vol. xi, Otol. Section, p. 21.

combat, airmen are liable to breathe with mouth open. The throat is then apt to get parched and swallowing becomes positively fatiguing or well-nigh impossible. If this occurs and the normal regulating mechanism for opening the eustachian tubes prove unequal to the task, the airman experiences considerable discomfort, often intense pain, and sometimes is in great distress. The symptoms may be only momentary or they last for some time after landing: one frequently sees airmen, just returned from high flights, put the fingers to the ear and press on the tragus several times, or else try to self-inflate the ears after landing; I found the drums invaginated in these cases. Swallowing is often ineffectual in opening up the lumen, probably owing to swelling from hyperaemia of the mucosa lining the eustachian tube. Sometimes this occlusion of the eustachian tubes lasts for hours, days, or weeks, during which period flying increases the deafness and discomfort or pain.

Clinical Records.

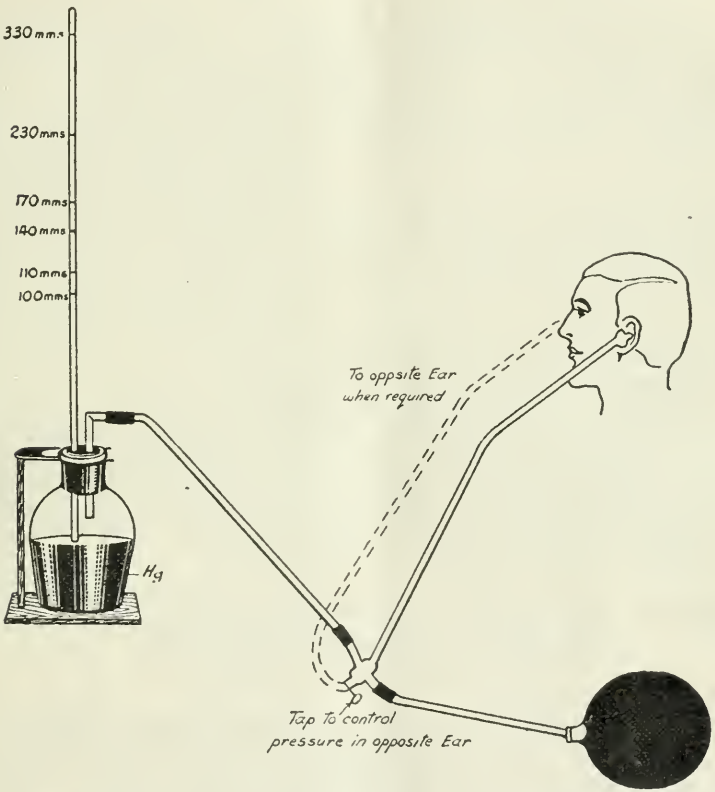
Case 17. Lieut. H. H. S. F. was a flying officer of one and three-quarter years' experience, with 200 hours flying including 150 on active service. In February 1918, when on a Sopwith Camel (Bentley Rotary 170 h.p. engine) while chasing an enemy machine, he dived with engine on, from 18,000 to 1,000 ft. He was conscious of greatly increasing pressure sensations in his head and deafness, which he failed to relieve by repeatedly swallowing as usual. The pressure caused pain in the ears which became more and more intense. He felt 'as though his head would burst', and being incapable of catching his enemy, broke off pursuit and returned to his aerodrome, in such pain that he at once went to a casualty clearing station. Unfortunately, the medical officer had no instruments to examine the ears, but he recommended him to have them syringed; however, this gave no relief. He endured the pain which lasted four or five days and there was a slight discharge, which lasted a few weeks. Subsequently, when on leave to England, it was discovered that the right tympanic membrane was ruptured. In April the rupture could be seen in the quadrant nearest the eustachian tube; I kept this officer under my care until the rupture healed and, having taught him how and when to self-inflate both ears, allowed him to return to duty with his squadron near Dunkirk. There was then no obvious deafness, and the hearing tests showed the merest defect in the right ear.

Hearing tests.	*Right.*	*Left.*	
Tone range.			
Lowest	16 d.v.	16 d.v.	Bezold-Edelmann,
Highest	0·3	0·2	Galton-Edelmann whistle.
Tone acuity.			
(Mixed sounds) Watch .	10 in.	15 in. (normal—15).	
(High pure tones). c^5 fork, 2 seconds, normal.			
Weber's test, fork on vertex heard louder in the right ear.			

I was informed by Lieut.-Colonel Birley that this officer subsequently did well after resuming flying duties and had no further trouble with his ears, which he was careful to inflate during descents.

Laboratory Tests of the Effect of Compression of Air in the External Ear.

To test the sensations of variable air pressure on the drum I adapted a mercurial sphygmomanometer and connected it by thick walled rubber tube to a nozzle which accurately fitted the external auditory meatus. With this arrangement one could compress the air in the external auditory canal on to the drum, and read the pressures attained in millimetres of the column of mercury. Having first tested the effect of compression on myself, I applied it to others and



soon found the tolerance to pressure varied among different individuals. Some could not bear more than 140 mm.[1] on the first occasion without pain, but after repeated trial the threshold was raised to 170 mm.[2] Others found 280 mm.[3] the first time quite tolerable. The first symptom of increasing pressure was deafness ; as the pressure was raised the discomfort passed on to acute stabbing pain in the ear.

A few individuals noticed distinct dizziness when high pressure

[1] This would correspond with the excess of atmospheric pressure on the drum produced by a rapid descent from about 6,000 ft. to near sea-level, with eustachian tubes remaining closed

[2] Corresponding to descent from nearly 7,000 ft., eustachian tubes keeping closed.

[3] Corresponding to descent from nearly 13,000 ft,. eustachian tubes keeping closed.

was applied to one ear at a time, but no dizziness when both ears were equally compressed.

A pressure limited to 320 mm. Hg was insufficient to rupture the drum of the cadaver—(both ears were tested in ten cases to ascertain this point).

The rapid descent from 18,000 ft. which caused the drums to be ruptured in the flying officer, whose case is described above, would correspond to a pressure of about 350 mm. Hg, a pressure not applied in the laboratory.

A Case of Haemorrhage of the Drum due to Rapid Descent.

Case 4. Second Lieut. C. R. C. had flown about 50 hours in France, and 110 hours in all. He was flying Sopwith Camels (La Rhone engine), had been in six combats, and had shot down one enemy aeroplane. During an air fight in the middle of March 1918, when he had a cold in his head, he dived nearly vertically with engine on at 200 m.p.h. from 15,000 to 3,000 ft., becoming conscious of great pressure on his ears, and with a feeling as if his head would burst. The pain in the left ear was severe for two days : it passed off gradually. Three weeks later, when I saw him, he still had a small dry clot of blood adherent to the antero-inferior quadrant of the drum, but there was no perforation. He had recovered from the cold in the head and could now auto-inflate both ears. Soon afterwards he returned direct to his squadron in France.

Conditions similar to those met with in Cases 17 and 4, recorded above, have been erroneously regarded as being due to otitis media, the result of a ' cold in the head ' instead of what they primarily were—namely, traumatic rupture from excessive air pressure on the outer surface of the drum : the ' cold in the head ' having prevented the regulating function of the eustachian tubes.

Appearance of Tympanic Membrane after Descent from 17,000 *ft.*

(*a*) When eustachian tubes fail to open.

(*b*) When eustachian tubes open.

Exemplified by Case 98.

Flight Sergeant W. F. P. was a test pilot, who was considered by his fellow officers to be ' breaking up ' in health and would have to give up tests above 12,000 ft., because he always seemed to feel so ' bad ' when he landed. They supposed this was due to ' heart trouble ', but the medical officer found the heart normal.

On May 9, 1918, at 7 p.m., I saw him land a Bristol Fighter in which he had been up to 17,000 ft. for an hour. He admitted to his friends he felt ' off colour ' but to the medical officer said ' he felt alright ', except that ' his head was throbbing a bit ' and ' of course ' he was ' deafish '. This was not obvious during conversation, but he could only hear a watch when within 4 in. from the right ear and 8 in. from the left, which was one-quarter and one-half the full hearing distance for this particular watch. He was persuaded to allow me to examine the drums of the ears. I found they looked bright red : the blood vessels could be seen to be distended and the whole drum was tensely invaginated and moulded over the ossicles

and inner wall of the tympanic cavity, in the lower part of which three or four small globules of clear fluid could be seen. (Similar cases had been sent to me with the diagnosis of ' chronic perforation ' —' drum destroyed '.)

He tried unsuccessfully to inflate the ears, holding the nose and blowing by Valsalva's method, but desisted because this made the pain in the ears worse. (I found this a very general experience.)

He had no intention whatever of ' going sick ', nor was it suggested he should. He gave me the impression of being cheerful, stoical, and regarded the discomfort, defective hearing and throbbing in the head, as ' nothing unusual ', and declared he would probably be all right the following day. He readily submitted to be a subject for further examination, and when it was found that politzerisation failed to open the eustachian tubes he allowed me to pass the eustachian catheter and inflate the ears. The pain in the ears was removed and the drums were seen to have returned to the normal attitude ; his instant relief was obvious.

He quickly learned to self-inflate both ears at will, whether flying or not, and found by this means he could prevent what now he admitted had been intense discomfort and pain sometimes lasting for days, though he had hitherto regarded these ' unpleasant feelings ' as necessarily associated with high flying.[1]

A spirit of determination to tolerate discomfort uncomplainingly was the rule in the same unit, for four out of the other five test pilots were found to be similarly affected, returning from flights to 16,000 and 20,000 ft. with deafness and drums invaginated.

They were treated in similar manner and were taught how self-inflation prevented this distress : and were enabled to make flights to 20,000 ft. returning quite free from the ear symptoms, and with normal looking drums, and feeling fresh, so that they no longer had to go and lie down after flying. It was particularly striking in one test pilot who made two ascents to 20,000 ft.[2] with no rest in between, which he had never done before in his life, without experiencing the discomfort and headache he had hitherto regarded as inevitable after each altitude test.

Vertigo and Inco-ordination.: and Unilateral Eustachian Obstruction.

Case 6 (*Summary*). *Recently dived from* 11,000 *to* 1,000 *ft. : deaf : later found flying difficult and apt to get into a spin. Vertigo, staggering gait. Eustachian obstruction and middle ear deafness. Recovered after catheterization.*

Lieut. I. B. C. was a flying officer who had been in France two and a half months, during which time he had flown about sixty-five hours. On one occasion, when returning from patrol duty, he made a side-slip dive from 11,000 to 1,000 ft. and the ears felt ' as

[1] I ascertained that subsequently this officer tolerated high flying without the discomforts and ill effects he had experienced formerly, and which threatened to terminate his flying duties.

[2] Clockwork barographs were carried on these machines to record the heights attained.

if they were plugged'. After this he had found even ordinary flying difficult, and had returned from flights unusually tired and sleepy. He had especial difficulty in co-ordinating his controls, 'always putting on too much rudder and not enough bank', and was losing self-confidence. Faulty flying had caused him to come down in a spin, though he managed to pull out in time to prevent a bad crash, staggered to his hut, and was later seen by the medical officer who sent him to the hospital. I found he had rhinitis and obstruction of the left eustachian tube. He could not auto-inflate the left ear but he could inflate the right; doing so made him feel giddy and he nearly fell off his seat.

The tympanic membrane of the left ear was then only slightly invaginated and a dusky red reflex showed the mucosa of the middle ear to be hypervascular. When a catheter was passed into the left eustachian tube and air was blown into the middle ear, he suddenly exclaimed 'I'm going off', shut his eyes tightly and gripped hold of the chair, but his lips were not pallid and his pulse was strong. At the same time forced movements of the head and neck-muscles commenced, causing the face to turn toward the left with flexion of the head to the left and backward extension. He felt 'as if he was 'falling to the right, and that the room was tilting down to the left'. All these sensations passed off in less than a minute. He recovered from the rhinitis and eustachian obstruction and was, on account of enlarged tonsils, recommended for leave to England before returning to duty.

Unilateral Eustachian Obstruction causing Vertigo with so-called Nerve Deafness.

Case 21. Vertigo, vomiting, so-called *nerve-deafness*, nystagmus, rhombergism, forced reeling gait, eustachian catarrh; complete recovery and return to active flying duties as test pilot.

Lieut. A. B. T., a Canadian; was a test pilot who had been in France about two months. He had a slight cold in the head and had merely tested the air-speed of a Sopwith Camel at between 2,000 and 3,000 ft., without rolling or spinning the machine; on landing he felt sick and giddy, and afterwards went to his quarters and lay down for a few hours. In the evening he was well enough to go into mess. After breakfast the following morning, while in an S. E. 5 warming up the engine, he again felt giddy. He switched off the engine, climbed out of the machine, staggered to his hut, and vomited. He remained in bed for twenty-four hours without food, the giddiness persisting and being worse when he moved his head or attempted to get up. Five days later he was sent to hospital, where he was overhauled by the late Lieut.-Colonel Corbett, who, finding he could not hear a watch with the left ear, asked me to examine him.

As he entered the room I noticed he walked slowly with outstretched arm, apparently apprehensive of falling. While seated he inclined the head to his left, though he said he was quite unaware of doing so. While I held his head straight he said it felt inclined to the right, and I observed both eyeballs slowly rotate about an

antero-posterior axis, clockwise, to the left to take up their original position in space. Moreover, when the eyes were deviated towards the right, fine rotary nystagmus appeared with the rapid jerk counter-clockwise, i. e. upper meridian of the eyeball, to the right. There was no nystagmus when the visual axis were directed towards the left. When released the head again slowly inclined to the left, resuming its original position of left lateral flexion.

On attempting to stand with eyes shut with feet close together the patient fell towards the left. He also lurched heavily to the left when attempting to walk straight, with eyes closed, the line followed being some forty-five degrees away from the straight line he had intended to follow. There was nothing else abnormal discovered in the general neurological survey. The *tympanic membranes were perfectly normal in appearance*, with absolutely no displacement inwards or outwards and no hyperaemia. However, he could not auto-inflate the left ear, although he could inflate the right, by Valsalva's well-known method.

Tone range.	*Right.*	*Left.*
Lowest audible . . .	16 d.v.	24 d.v. (Bezold fork).
Highest audible . . .	0·6 mm.	1·6 (Galton whistle).
Tone acuity.		
(High pitch watch) . . .	8 to 12 in.	nil (normal 12 to 15 in.).
c^5 fork	normal	— sec.
Schwabach-conduction . .	normal	Slight loss of bone conduction.

(Rinne method) air conduction better than bone on each side.
(Weber's method) bone conduction from the vertex louder in the right ear.

These tests indicated a condition often so-named ' nerve-deafness ' in the left ear.

Air was inflated through a catheter into the eustachian tube on each side, first the right, which increased the hearing acuity for the watch, but produced no effect on the giddiness; when air was blown through the catheter into the left eustachian tube, fluid *râle* was audibly produced in the left middle ear. The blowing was continued until the *râle* was displaced by the clear sound of air entry, and the catheter was then removed. The patient immediately exclaimed that the giddiness had ceased; as evidence of this he could stand and walk straight with eyes shut, there was no lateral flexion of the head, and it was seen as objective evidence that the nystagmus had disappeared. The hearing for lowest tones 16 d.v. was equal on the two sides, and in Weber's test the bone conduction was equalized, but the hearing for high tones at first improved hardly at all. Next morning the symptoms of giddiness, together with all other signs described above, recurred; and again the left ear could not be inflated without the catheter, which on this occasion also put an end to the giddiness instantly. The catheter was necessary, for the same reasons, on the third day, after which the patency of both eustachian tubes came under the patient's control, for he was now able to inflate both ears equally and has ceased to be troubled with giddiness since. Instead of his being transferred to England as an invalid, I recommended that this officer be allowed to return direct to flying duties without restriction, and a few days afterwards he ferried a captured Hanover two-seater to Farnborough, bringing back a new S. E. 5 two days later, and subsequently carried out his

ordinary test-flying up to 16,000 and 20,000 ft. without any recurrence of symptoms.

Two points in his history were brought out afterwards. Firstly, he had had a cold in the head about a fortnight and for ten days had felt slightly giddy when flying without having complained. His fellow officers told me they had noticed he was not flying as well as usual for ten days, and, in fact, had told him that he would crash because he was *flying and landing with the left wing lower than the right even when direct into the wind.* After the treatment described above he flew quite level, as I saw for myself. These observations fully tally with the signs of inco-ordination and forced movements which I noticed when he came to the hospital. The importance of the foregoing case in connexion with crashes of unknown origin deserves full recognition.

Vertigo and Nystagmus, associated with Obstinate Eustachian Obstruction, reproduced by Pressure Changes in the Middle Ear.[1]

Case 129. Lieut. G. F. S. This officer was sent to me on account of deafness in the left ear, which was worse after flying and had been increasing for some months past. He had also had occasional attacks of pain especially during descents, and he had felt dizzy several times when landing. He had been in France since March 1918 with a squadron engaged principally in artillery observation and rarely flew above 9,000 or 10,000 ft.

At the time of examination, in May 1918, he had no pharyngitis or rhinitis, but the eustachian obstruction was so marked that for a week it defied all attempts to blow air into the middle ear, in spite of the use of the eustachian catheter, bougies, and the application of cocaine, adrenalin, atropine, menthol inhalations, and the administrations of iodides and aperients. The right ear was always easily self-inflated, and there was no special difficulty in introducing the catheter into either eustachian tube. Every day the drums were inspected before and after these attempts, but the left drum remained unmoved in a position of invagination ; the mucosa of the middle ear could be seen to be hyperaemic through the transparent membrane.

On the eighth day, air blown through the catheter could be heard entering the tympanum by means of the auscultatory tube. At the same moment, the patient felt giddy and there were manifest forced, jerking movements of the head and nystagmus.

When the inflation was weak, the head was inclined, and face turned to the right, and the nystagmus (combined horizontal and rotatory) was to the left.

Stronger inflation—distending the tympanum—caused the forced movements of the head and eyes to be reversed.

It was over three weeks before this patient succeeded in self-inflating the left ear and he was afterwards transferred to England,

[1] By permission of the Director General, I was permitted to record this case in the *Journal of Laryngology, Rhinology, and Otology,* February 1919, vol. xxxiv, No. 2, p. 51, where a fuller account would be found.

and though he flew again, he was, I understand, eventually invalided out of the Air Force, owing to the persistent ear trouble and impossibility of self-inflating the left tympanum.

Concluding Remarks to Part I.

The foregoing clinical cases are selected from over 300 records of officers examined in France. They serve to illustrate the outstanding importance of efficient eustachian tubes, whereby an airman should be able to correctly regulate and equalize the continuous changes of atmospheric pressure experienced in flights from low to high and from high to low altitudes.

These cases also serve to show that the deafness and distress in the ears which occur through flying are the result of inefficient eustachian tubes, and that these symptoms are preventable. And lastly that vertigo and vomiting and forced movements, which interfere with the proper control of an aeroplane, are sometimes induced by the unequal pressure in the ears, resulting from unilateral eustachian obstruction, and that such symptoms are overcome by removing the cause.

How to prevent Giddiness, Deafness, and Earache due to Descents from High Altitudes.

The following rules were proposed to Lieut.-Colonel Birley as a result of my experience among airmen in France:

(1) That airmen should not fly with a cold in the head, sore throat, or when unable to inflate both eustachian tubes at will.

N.B. Airmen with large bilateral perforations of the tympanic membrane did not feel the ear symptoms experienced by those with normal drums. Contrary to the usual practice I recommended they be permitted to continue flying duty which they carried out with success.

(2) Airmen who can open the eustachian tubes at will by swallowing should use chewing gum to stimulate the flow of saliva and keep swallowing, especially while descending.

(3) Airmen who cannot rely upon swallowing, to open the eustachian tubes repeatedly and rapidly, should make a rule of self-inflating the ears by Valsalva's method and should *begin to do so at the commencement of the descent—repeating the procedure* once, say every 1,000 ft., and not wait until they land.

(4) All may practise, though few succeed, in the following procedure:

Open the mouth slightly while trying to maintain the lower incisor teeth as far in front of the upper as possible. The effort can only be strongly sustained for a minute or less: one should be conscious of tightly contracting the muscles of the palate and upper pharynx at the same time. If the procedure succeeds, one can pass through considerable changes of atmospheric pressure, without having to swallow or inflate the ears, as the walls of the eustachian tubes are

kept apart for an appreciable time by this voluntary muscular action alone.

2. Part played by the Semi-circular Canals in Aviation.

It has been assumed, but never proved, that a pilot is dependent upon the sensitiveness of the semi-circular canals to maintain equilibrium when flying. Yet a person whose semi-circular canals have all been removed on both sides, can run and ride, dance and turn, hop and jump with eyes open or shut, and presumably could learn to fly. These extreme views we shall have to reconsider in the light of investigations made on airmen in the Air Force in France during the War.

The clinical methods of investigating the semi-circular canals have been applied to airmen. The tests employed in clinical practice depend upon the fact that normal semi-circular canals can be so stimulated, artificially, that they set up certain characteristic reflex movements which differ in intensity in different individuals. Semi-circular canals destroyed by disease are of course irresponsive to even the strongest stimulating agents. We can thus ascertain whether each canal is responding to stimulus or not, and so can recognize diseased conditions.

The methods of stimulating the semi-circular canal system employed clinically are as follows :

1st. Rotation with sudden deceleration.
2nd. Thermal (hot or cold water or air).
3rd. Pressure (limited to certain conditions only).
4th. Galvanism.

Clinical methods have been applied to airmen, in order to ascertain and compare the intensity of the reactions which are so set up, and which are described later, probably in the first instance on purely hypothetical grounds.

For we must believe that the assumption was that a pilot depended largely on the semi-circular canal system to maintain his own equilibrium and that of his aeroplane.[1]

In investigating disorders of the central nervous system, and of certain diseases of the ear, it is often necessary to employ *all* these methods before an accurate diagnosis can be made. In this paper I shall confine my observations to rotation and caloric tests as applied to airmen, because these tests have been employed by other medical officers in the selection of candidates for the Flying Services and in grading flying officers according to the different reactions displayed.

Normal Phenomena produced by Rotation.

The individual is rotated in a chair or a turning stool, or a seat suspended from a beam, or, failing these appliances, simply on the feet, round and round, a certain number of times at a certain rate

[1] *Vertigo and Equilibrium*, by Major Isaac Jones, M.D., American Aviation Service (Lippincott, 1918).

and then suddenly stopped. This sudden stop after turning (i. e. *deceleration*) causes dizziness, which varies in degree and duration in different persons, and is accompanied, according to the strength of stimulus, by forced movements of eyes, head, and limbs.

The direction and character of nystagmus and other forced movements, and the kind of subjective sensations depend upon the *position of the head,* while being turned, and on its being maintained in the same constant position throughout the turning and at the moment when the head is brought to a sudden standstill.

The rate of rotation should not be less than one turn in four seconds, otherwise the stimulus is insufficient to evoke the phenomena sought for. As a rule, from five to ten turns are necessary to produce a definite effect. The same rate should be observed in making both clockwise and counter-clockwise rotation.

Three different positions of the head during turning are adopted.

First Position—Head erect. Care should be taken that the chin is depressed (the mouth being closed) and the face is not elevated ; otherwise, the superior semi-circular canals will respond in place of the external canals. For instance, a normal subject with head in position for stimulating external canals will deviate to the right after clockwise rotation, whereas if the head is too erect, so that the superior canals receive part of the stimulus, he will deviate and lean to the left after clockwise rotation. After being turned, six to ten complete revolutions, the individual attempts to walk straight, with eyes shut ; it can be seen that many individuals, when told not to resist, will tend to walk circuswise, where space permits, in the same direction as the rotations were made. Instead of attempting to walk, he may try to point, as Bárány explained, in a prearranged direction with hand or foot, when the ' normal error of deviation ' due to rotation stimulation can be observed.

The nystagmus is ' horizontal ' and greatest when the eyes are voluntarily turned opposite to the direction of rotation ; its duration varies in different persons.

Second Position—Face directly downwards. Five turns in fifteen seconds usually suffice to produce a response. On stopping the turning as before, the individual rises with head erect and is directed to try and walk straight. Some will succeed, with eyes open or shut, others will stagger to the ground, unable to rise for perhaps half a minute or longer. The nystagmus, which must be sought for quickly, will be seen to be fine and rotatory, with the more rapid jerk of the upper meridian of the eyeball away from the direction towards which the previous turnings were made. There is a considerable difference in the duration of nystagmus, in seconds of time, among different groups of individuals in health.

Instead of attempting to walk directly after being turned, the subject under examination can try to hold the head erect, with eyes shut, and extend both arms laterally level with shoulders ; he will involuntarily hold one arm more or less above, and the other below the horizontal level, the head and trunk showing a tendency, more or less marked, to incline laterally towards the lower side. The sensations to an airman somewhat resemble those associated with ' banking '.

Third Position during rotation—With the right side of the head downwards, and face forwards, the sagittal plane of the head being maintained as horizontally as possible. The turnings are made first counter-clockwise, the face travelling forwards, and then clockwise. Five or six turns in ten or twelve seconds are usually sufficient to provoke a response and reaction, for directly the head is raised into the erect position after stopping, emprosthotonus or opisthotonus is set up, according to the direction of rotation, counter-clockwise or clockwise. The nystagmus is of short duration and is upwards in the former and downwards in the latter case.

The sensations of the normal individual produced by rotations in the third or lateral position have been compared by airmen to those experienced in ' zooming ' on the one hand and ' nose diving ' on the other, as soon as the head is raised to the erect posture.

Among any considerable number of normal persons, we shall find some who experience no disagreeable sensation whatever after being turned, with head in any position. Others are intensely giddy only after being turned with face down or up.

The result of turning in the erect position is an unreliable indication of the degree of reaction likely to be produced by turning with face down or sideways; in consideration of this point it should be remarked that it has been the custom to alter the position of the head and resume the erect position after turning in the second and third positions, whereas the head is maintained in the same position in relation to space both during and after rotation, in the first position. [In reapplying clinical tests this point will probably need further investigation.]

The above-described phenomena are the usual result of hyper-stimulation by rotation in normal persons. They do not occur after destruction of both vestibular end-organs, and they are markedly asymmetrical in patients who have unilateral destruction of the semi-circular canals.

Caloric Test.

As is well known, the application of cool or tepid water to the drum of the ear abstracts heat from the tympanic cavity and, more slowly, from the outer wall of the labyrinth: the endolymph and perilymph will condense and so convection currents are set up in the superior semi-circular canal when the head is erect (and in the external semi-circular canal if the face is either upwards or downwards).

The reactions obtained by these caloric tests with head erect are similar in character to those obtained by rotation stimuli with the head in the face-down position. (See p. 41.)

The caloric test can, however, be applied to one side at a time, and the reaction obtained can be compared with that provoked by applying the test to the opposite ear.

Normal individuals with normal drums and normal eustachian tubes react equally strongly whether the right or left ear is stimulated, provided the temperature of the water and the rate of flow is constant.

When I went to France I found some airmen who had been admitted to hospital with giddiness associated with deafness had been already

subjected to the caloric tests, even when the drums were intact; the method employed being that of irrigating the external auditory canal in the usual way with tepid water for one or more minutes until nystagmus or dizziness was induced, the head being kept erect.

It so happened, however, that in the airmen mentioned above, the reaction was unequal, being stronger in some when the test was applied to the affected ear, as compared with the normal ear, and in others weaker when applied to the affected ear.

I was already aware that any person whose drum was invaginated reacted more readily to the caloric test applied to that side than to the normal side—for the simple physical reason that the drum being closer to the labyrinthine wall, the heat was abstracted more quickly by the irrigating stream than when a cushion of air intervenes.

Further, hypervascularity of the drum or lining membranes and the presence of mucus in the tympanum retard the reaction to the caloric test.

It was for these reasons that I did not employ this test as a routine in the case of airmen—although it is one of great service in the investigation of the labyrinth in diseases of the central nervous system and in some cases of suppuration in the middle ear, when we desire to ascertain simply whether there is a response or no response.

Results of Rotation. Tests in France.

In order to obtain first-hand data on the relation between rotation reactions and flying ability by the application of the clinical labyrinthine tests to flying men, I made notes of a series of sixty-two pilots and observers, among whom were twelve high-grade and experienced pilots—all of whom volunteered to submit to the examination.

I relied chiefly upon the tests to observe the activity of the forced movements, in so far as rotation-deceleration interfered with the attempt to walk straight, immediately after turning.

The sensations of disturbed equilibrium and of induced giddiness were also inquired into and noted.

It seemed unavoidable that a mathematical formula must give way to some such convention as can be expressed by the terms:

Forced Movements—Absent or Slight. Group 1.
Forced Movements—Moderate. Group 2.
Forced Movements—Strong. Group 3.

In Group 3, shown in Table I, 'strong forced movements' after rotation, cases are included in which rotation caused the individual to collapse to the floor, from which he could not rise for several seconds at least; and those who staggered so much while attempting to walk that they failed to approach a previously selected mark. It is interesting to notice that this group included some 'crack' airmen who will be further alluded to.

TABLE I.

Rotation type.	*Forced movements.*	*Giddiness.*	*Number tested.*
A.	Absent or slight	Slight	21
B.	Moderate	Slight	17
C.	Strong	Slight	8
D.	Absent or slight	Moderate	—
E.	Moderate	Moderate	6
F.	Strong	Moderate	2
G.	Slight	Intense	3
H.	Moderate	Intense	4
J.	Strong	Intense	1

First grade pilots 12. Observers and other pilots 50. Total 62.

The first group—'forced movements: absent or slight'—was designed to include those who walked rapidly to the chosen mark, without showing more than a mere waver; this also included some of the best fighting airmen of their day. (See A. D. G., Tables I and II.)

The 'moderate group' included those who, after a definite détour, managed to gain the point sought for without an apparent struggle. (See B. E. H., Tables I and II.)

In estimating the individual's category, most reliance was placed on the result of the face-down test.

In Table I we notice that *giddiness* was not always in proportion to the 'activity of the forced movement'. It is certain that, as in Type C, there are always some individuals who are averse from admitting feeling giddy, while in Type G we meet with others who feel giddy and every motion when in the air as in the rotation-chair and are regarded as 'temperamentally unfit', though they do not show strong 'objective' reactions in the rotation-chair.[1]

TABLE II. (*First Grade Pilots only.*)

Rotation type.	*Forced movements.*	*Giddiness.*	*Number tested.*	
A.	Absent or slight	Slight	6	Capt. No. 1, Capt. No. 15, Capt. No. 55, Capt. No. 16, Capt. No. 64, Gen. L.
B.	Moderate	Slight	3	Capt. No. 19, Capt. No. 42, Capt. No. 43.
C.	Strong	Slight	—	
D.	Absent or slight	Moderate	—	
E.	Moderate	Moderate	—	
F.	Strong	Moderate	1	Capt. No. 25.
G.	Absent or slight	Intense[2]	—	
H.	Moderate	Intense	1	Capt. No. 14.
J.	Strong	Intense	1	Major No. 81.

[1] The chair employed was lent by the United States of America Aviation Medical Service through the courtesy of Lieut.-Colonel Isaac Jones, and was similar to that in use in America, by the medical officers for the examination of candidates for the Air Service.

[2] i.e. giddiness with shock reactions, pallor, clamminess, small pulse—headache, nausea lasting a quarter of an hour or longer.

TABLE III. [*Type A.* (See Table II.)]

Rotation test.	*Position of head.*	*Direction of rotation.*	*Number of turns.*	*Induced rhombergism.*	*Effect of gait.*	*Sensations of orientations, &c.*	*Intrinsic sensations, dizziness, nausea, &c.*
1	Erect	Clockwise	6	No	Slight curve to right	Room going round horizontally to left	Momentarily giddy—no nausea.
2	Erect	Counter-clockwise	6	No	Slight curve to left	Room going round horizontally to right	Momentarily giddy—no nausea.
3	Face down	Clockwise	6	Falling to right	Staggered slightly and leaned to right, but kept nearly straight course	Floor seemed to bank to left on facing forwards, eyes open	Momentarily felt as if spinning to left. Slightly 'giddy' for few seconds.
4	Face down	Counter-clockwise	6	Falling to left	Staggered slightly and leaned to left, but kept nearly straight course	Floor seemed to bank to right on facing forwards, eyes open	Momentarily felt as if spinning to right. Slightly 'giddy' for few seconds.
5	Right side of head down	Clockwise	6	Falling backwards	Difficult to get out of chair owing to opisthotonos.	Seemed to be nose diving (when facing forwards)	'Not exactly giddy.' Conscious of strong forced movements. No nausea.
6	Right side of head down	Counter-clockwise	6	Falling forwards	Flexed head and trunk forwards	Seemed to be tail sliding when facing forwards	'Not exactly giddy.' Conscious of strong forced movements. No nausea.

Case 1, Capt. Case 55, Capt. Case 64, Capt.

TABLE IV. [*Type A.* (See Table II.)]

Rotation test.	*Position of head.*	*Direction of rotation.*	*Number of turns.*	*Induced rhombergism.*	*Effect on gait, &c.*	*Sensations of orientation, &c.*	*Sensations of dizziness, nausea, &c.*
1	Erect	Clockwise	—	—			
2	Erect	Counter-clockwise	—	—			
3	Face down	Clockwise	6	No	Walked straight, slight lateral flexion to right	Momentarily as if floor was tilted a little down to left	Not dizzy. No pallor, &c.
4	Face down	Counter-clockwise	6	No	Walked straight, slight lateral flexion to left	Momentarily as if floor was tilted a little down to right	
5	Right side of head down	Clockwise	—	—			
6	Right side of head down	Counter-clockwise	—	—			

Case 15, Capt. Case 16, Capt. Case Gen. L.

TABLE V. [*Rotation Type A. First Grade Pilots.* (See Table II.)]

Case No.	*Hours flown.*	*Remarks.*
1. Capt. . .	480	Flies Bristol Fighters at 17,000 ft. Credited with fourteen E.A.'s. Was once shot down in flames. Always descends very fast—dives, side slips or spins. When spinning in machine avoids looking over at ground, otherwise gets 'deadly giddy'. Not giddy if he keeps head in cock-pit.
		[Spads.]
15. Capt. . .	475	Flight Commander. fighting scouts. Great repute.
16. Capt. . .	325	Flight Commander, fighting scouts. Great repute. Very experienced horseman.
55. Capt. . .	650	Flight Commander, fighting scouts. Can spin 'camel' as many as eighteen turns to right, looking at ground whole time in drop of 6,000 ft. Once tried spinning to left and lost sense of position but managed to straighten out. Rotation tests, classified A. Pointing error normal. Good horseman.
64. Capt. . .	790	Flight Commander for fourteen months, fighting scouts. Can roll, spin, and do Immelmann's with ease, yet 'hates the sea like poison', 'always sea-sick'. Keen horseman. Rotation tests, classified A. Nystagmus and past pointing tests normal type.

TABLE VI. [*Rotation Type F.* (See Table II.)]

Rotation test.	*Position of head.*	*Direction of rotation.*	*Number of turns.*	*Induced rhombergism.*	*Effect of gait.*	*Sensations of orientation, &c.*	*Intrinsic sensations, dizziness, nausea, &c.*
1	Erect	Clockwise	7	Yes	Deviated to right	Room going round fast to left horizontally	Slightly dizzy. No nausea.
2	Erect	Counter-clockwise	7	Yes	Deviated to left	Room going round fast to right horizontally	Slightly dizzy. No nausea.
3	Face down	Clockwise	5	Strong to right	Could not walk at all for nearly one minute. Lay on ground on right side struggling to get up	Vertical bank and side slipping to left, when facing forwards after turning	Momentarily very giddy, rapid recovery. No nausea or pallor.
4	Face down	Counter-clockwise	5	Strong to left	Could not walk at all for nearly one minute. Lay on ground on left side struggling to get up	Vertical bank and side slipping to right, when facing forwards after turning	Momentarily very giddy, rapid recovery. No nausea or pallor.
5	Right side of head down	Clockwise	5	Strong backwards	Very strong opisthotonos	Nose diving (when facing forwards)	'Not exactly giddy'. No nausea.
6	Right side of head down	Counter-clockwise	5	Strong forwards	Strong emprosthotonos	Tail sliding (when facing forwards)	'Not exactly giddy'. No nausea.

Table VII. [*Rotation Type F. First Grade Pilots.* (See Table II.)]

Name.	*Hours flown*	*Remarks.*
25. Capt. . .	215	Fighting scout, Flight Commander. Has flown eight months. Credited with twenty-nine E.A.'s.[1] Is a dead shot. Aerobatics at early stage, but crashed many machines in learning to land scouts. Has flown to 22,000 ft. without oxygen. Never giddy or sick in air. Has been sea sick crossing Channel.

Table VIII. [*Rotation Type B. First Grade Pilots.* (See Table II.)]

Name.	*Hours flown.*	*Remarks.*
19. Capt. . .	900	A great and brave pilot credited with twenty-five E.A.'s. Can fly at 21,000 ft. without oxygen.
43 Capt. . .	480	Fighting scout, Flight Commander. Never giddy in air. Generally sick in boat. Began aerobatics early. Has twice collided in air, and safely landed in damaged machine.
42. Capt. . .	320	First flight as observer was sick in air—never since. Generally feels sick crossing Channel or Atlantic. Won M.C. for excellence of Corps work on R.E. 8's.

[1] Over twenty more since these notes were written.

TABLE IX. [*Rotation Type H.* (See Table II.)]

Rotation test.	*Position of head.*	*Direction of rotation.*	*Number of turns.*	*Induced rhombergism.*	*Effect of gait, &c.*	*Sensations of orientation, &c.*	*Sensations of dizziness, nausea, &c.*
1	Erect	Clockwise	6	No	Walked straight	Room going round to left horizontally	Giddy.
2	Erect	Counter-clockwise	6	No	Walked straight	Room going round to right horizontally	Giddy.
3	Face down	Clockwise	6	Slight to right	Walked almost straight	Felt as if spinning to left when facing down. Floor a little tilted down to left when looking ahead	Very giddy and nausea, slight pallor. Lasted several minutes.
4	Face down	Counter-clockwise	6	Slight to left	Walked almost straight	Felt as if spinning to right when facing down. Floor a little tilted down to right when looking ahead	Very giddy and nausea, slight pallor. Lasted several minutes.
5	Right side of head down	Clockwise	6	Falling backwards	Found it difficult to get up from chair	Felt as if nose diving	
6	Right side of head down	Counter-clockwise	6	Falling forwards	Found it difficult to prevent stooping forwards	Felt as if floor was coming up towards the face	

TABLE X. [*Rotation Type H. First Grade Pilots.* (See Table II.)]

Name.	*Hours flown.*	*Remarks.*
14. Capt.	700 at least.	Has flown since 1915. Credited with at least twelve E.A.'s. Fine pilot, but is 'not fond of spinning'. Prefers other manœuvres.

TABLE XI. [*Rotation Type J. First Grade Pilots.* (See Table II.)]

		Remarks.
81. Major.	Long experience, and a Squadron Commander of S.E. 5's in 1918.	Fine war pilot, leader and instructor of scout flying and fighting. 'Nearly always sea sick on sea: never while flying.' A keen dancer. He considered the effect in the rotation-chair *far exceeded* any induced by evolutions when flying.

Table II shows the results obtained from the First Grade Pilots only.

We find three exceptionally good scout pilots who showed strong forced movements or distressing giddiness, after slow turning. I would draw especial attention to Captain 25 [Tables VI and VII], who had already shot down twenty-nine enemy aeroplanes, and later was credited with nearly as many more. When this officer was turned five turns, even slower than was the average rate, he collapsed to the floor, after the face-down test, and struggled vainly to rise for fully half a minute. But he showed no signs of distress such as pallor, or clamminess of the skin, and had no headache.

Two other distinguished pilots with long war flying experience closely resembled Captain 25 in the reaction shown to hyperstimulation of the labyrinth by rotation, viz. Captain 14 [Table IX and X] and Major 81 [Table XI].

Both officers were absolutely normal men in their best flying form.

In contrast with the three above-mentioned officers, Nos. 25, 14, and 81, who reacted strongly, we can refer to the Groups A and B, which includes those whose responses were normal but the reactions were moderate, slight or absent.

None of these twelve pilots appears to have derived any assistance from the semi-circular canals to estimate position in space while flying, for they all admit losing the sense of position in dense clouds.

Conclusion.

Consideration of the data presented in the above Tables appears to show that the reactions to rotation may be excessive in some individuals and suppressed in others, but in neither case do the reactions of the semi-circular canals serve to indicate an airman's probable flying ability.

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